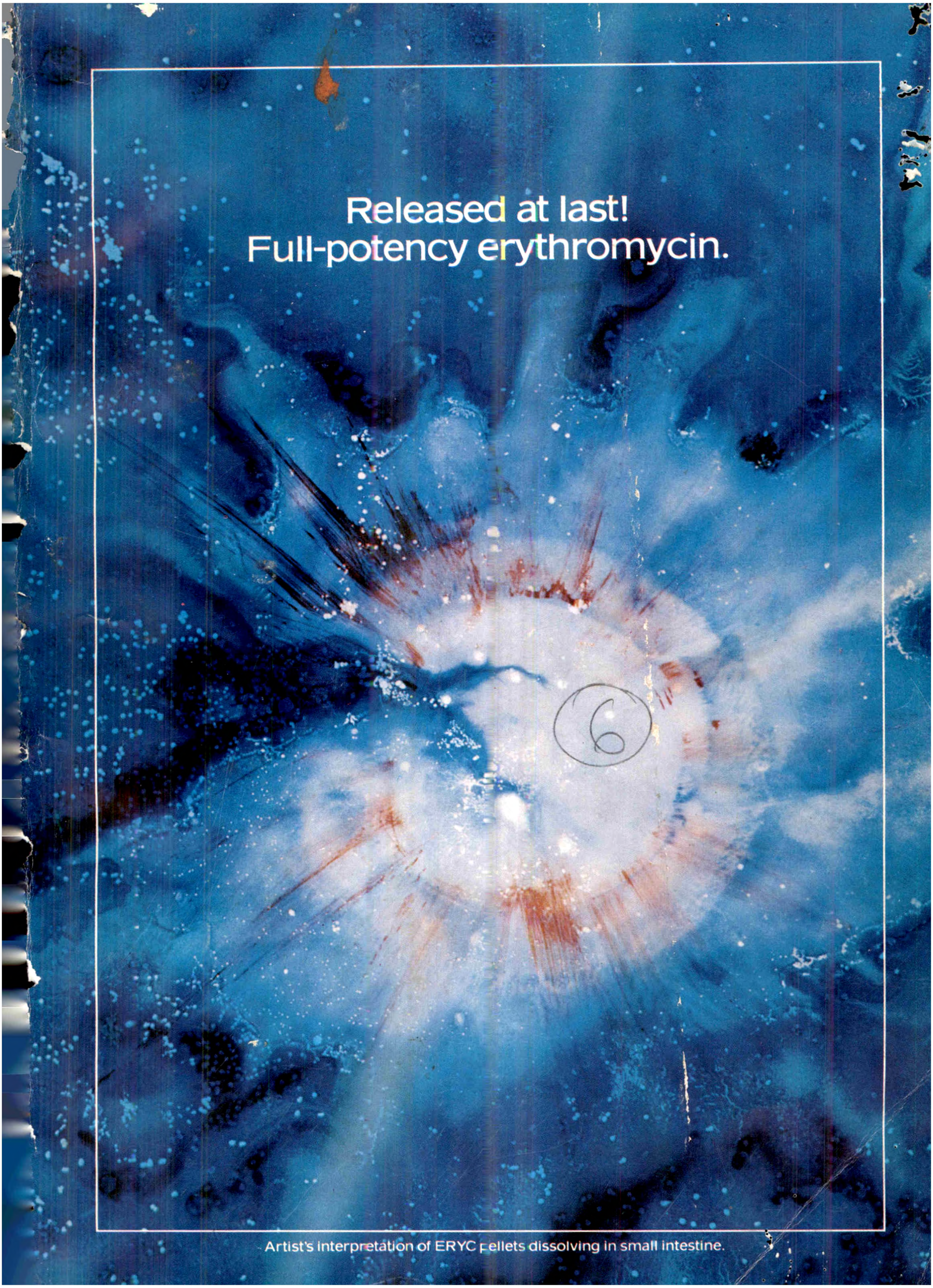
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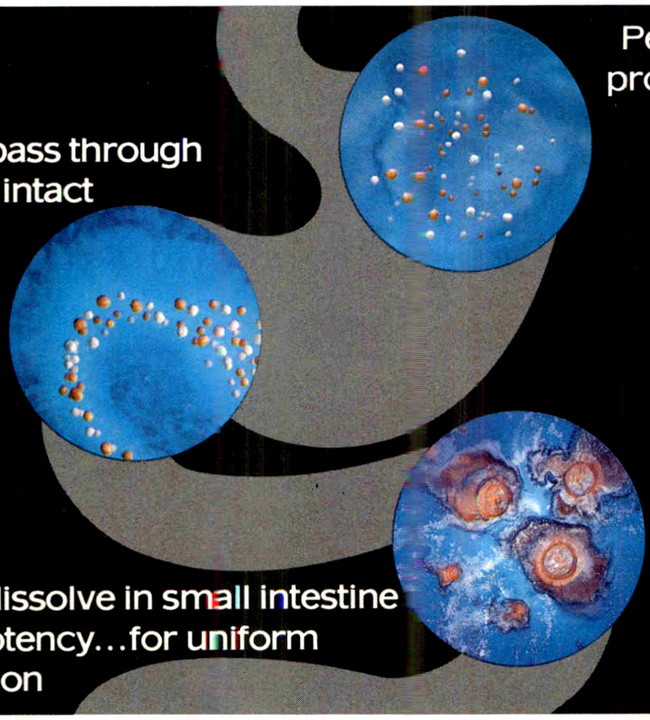

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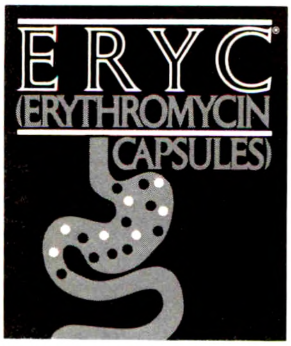

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Respiratory tract infections due to *Mycoplasma pneumoniae* (Eaton's agent).

Pertussis (whooping cough) caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

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Skin and soft tissue infections of mild to moderate severity caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (Resistant staphylococci may emerge during treatment.)

Primary syphilis caused by *Treponema pallidum*. Erythromycin (oral forms only) is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy. The use of erythromycin for the treatment of *in utero* syphilis is not recommended (See CLINICAL PHARMACOLOGY in full prescribing information).

Legionnaires' disease caused by *Legionella pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Therapy with erythromycin should be monitored by bacteriological studies and by clinical response (See CLINICAL PHARMACOLOGY—Microbiology in full prescribing information).

Injectable benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. When oral medication is preferred for treatment of the above conditions, penicillin G, V, or erythromycin are alternate drugs of choice.

Although no controlled clinical efficacy trials have been conducted, erythromycin has been suggested by the American Heart Association and the American Dental Association for use in a regimen for prophylaxis against bacterial endocarditis in patients allergic to penicillin who have congenital and/or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract. (Erythromycin is not suitable prior to genitourinary surgery where the organisms likely to lead to bacteremia are gram-negative bacilli or the enterococcal group of streptococci.)

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint 1977 statement of the American Heart Association and the American Dental Association.

CONTRAINDICATION: ERYC is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNING: There have been a few reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin ethylsuccinate, base, and stearate products.

PRECAUTIONS: Caution should be exercised when erythromycin is administered to patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and WARNING in full prescribing information).

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Pregnancy Category B—Reproduction studies have been performed in rats, mice and rabbits using erythromycin and its various salts and esters, at doses which were several times multiples of the usual human dose. No evidence of impaired fertility or harm to the fetus that appeared related to erythromycin was reported in these studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of ERYC on labor and delivery is unknown.

Nursing Mothers—Erythromycin is excreted in milk (see CLINICAL PHARMACOLOGY in full prescribing information).

Pediatric Use—See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS: The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatic dysfunction and/or abnormal liver function test results may occur (see WARNING).

Mild allergic reactions such as rashes with or without pruritus, urticaria, bullous fixed eruptions, and eczema have been reported with erythromycin. Serious allergic reactions, including anaphylaxis have been reported.

A few cases of transient deafness have been reported with high doses of erythromycin.

DOSAGE AND ADMINISTRATION: Optimum and uniform serum levels of erythromycin are obtained when ERYC Capsules are administered one hour before meals or in the fasting state.

Adults: The usual dose is 250 mg every 6 hours taken one hour before meals. If twice-a-day dosage is desired, the recommended dose is 500 mg every 12 hours. Dosage may be increased up to 4 grams per day, according to the severity of infection. Twice-a-day dosing is not recommended when doses larger than 1 gram daily are administered.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30 to 50 mg/kg/day in divided doses. For the treatment of more severe infections, this dose may be doubled.

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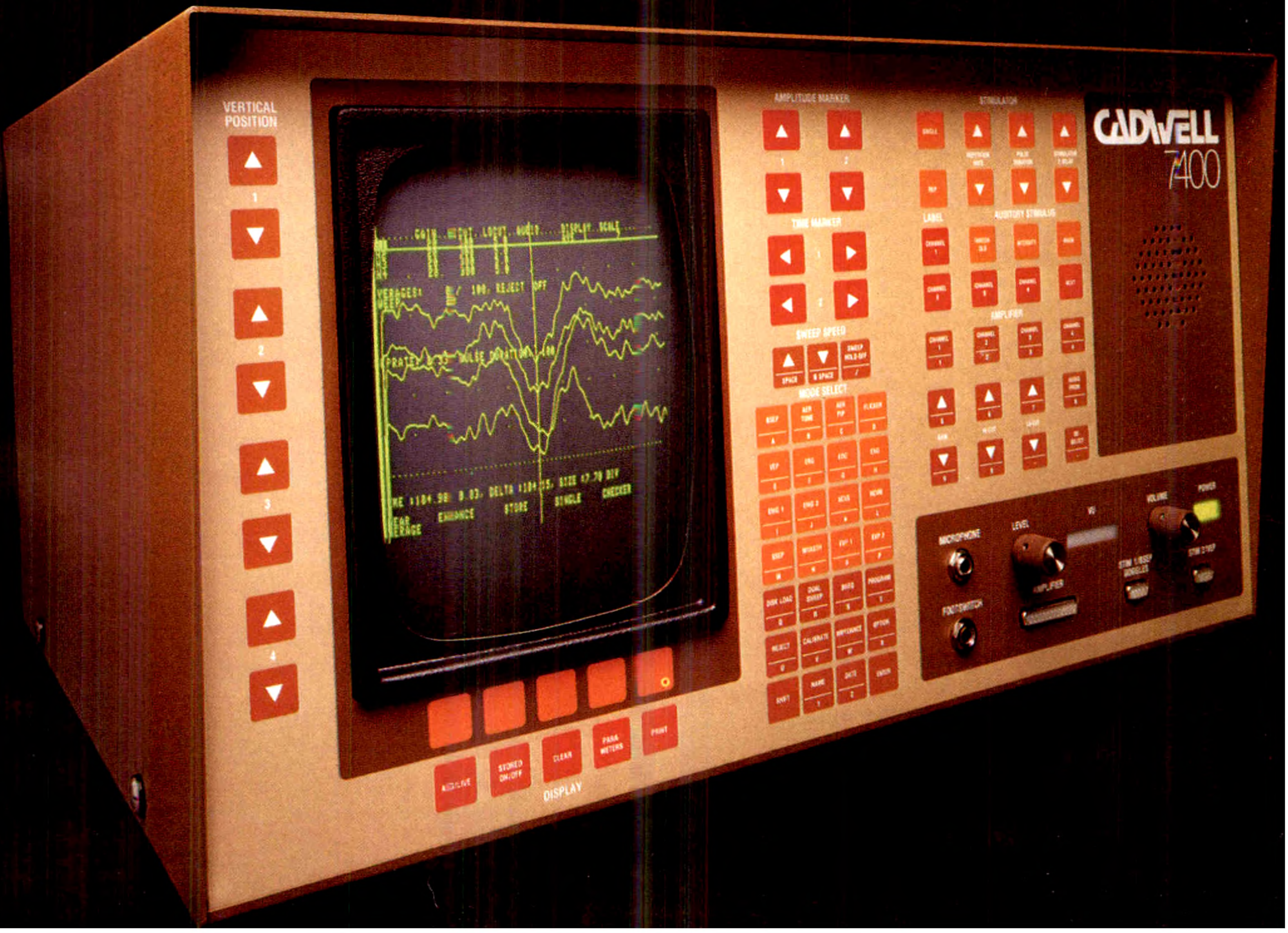

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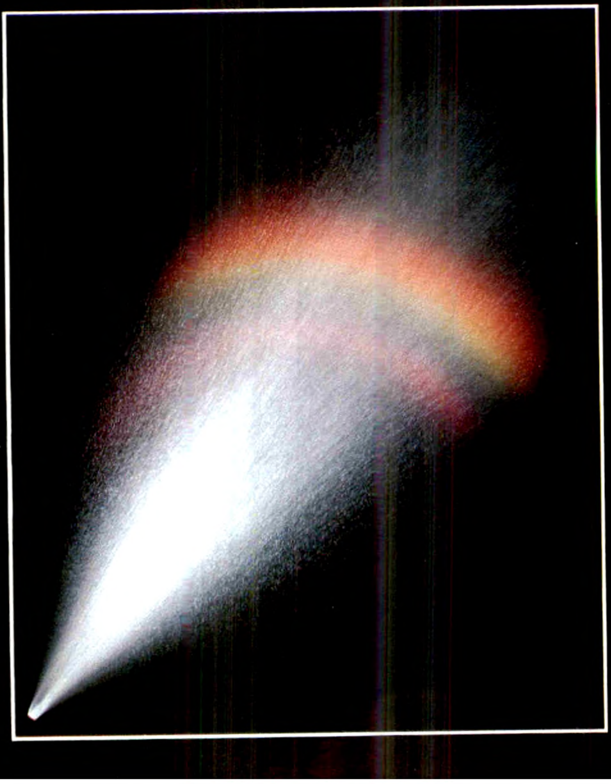

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Adverse Reactions: The most frequent complaints were mild transient nasal burning and stinging (reported in approximately 45% of patients). These complaints do not usually interfere with treatment; in only 3% of patients was it necessary to decrease dosage or stop treatment because of those symptoms.
Incidence of 5% or less: nasal congestion, sneezing, epistaxis and/or bloody mucus, nasal irritation, watery eyes, sore throat, nausea and/or vomiting, headaches and loss of sense of smell and taste. In rare instances, nasal septal perforations were observed during the studies but a causal relationship with Nasalide was not established.
Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, or if individuals are particularly sensitive, symptoms of hypercorticism could occur.
Dosage and Administration: Full therapeutic benefit requires regular use and is usually evident within a few days, but up to 3 weeks may be required for some patients to achieve maximum benefit. Patients should use a decongestant and clear their nasal passages of secretions prior to use.
Recommended starting dose in adults: 2 sprays in each nostril b.i.d. If needed, increase to 2 sprays t.i.d.
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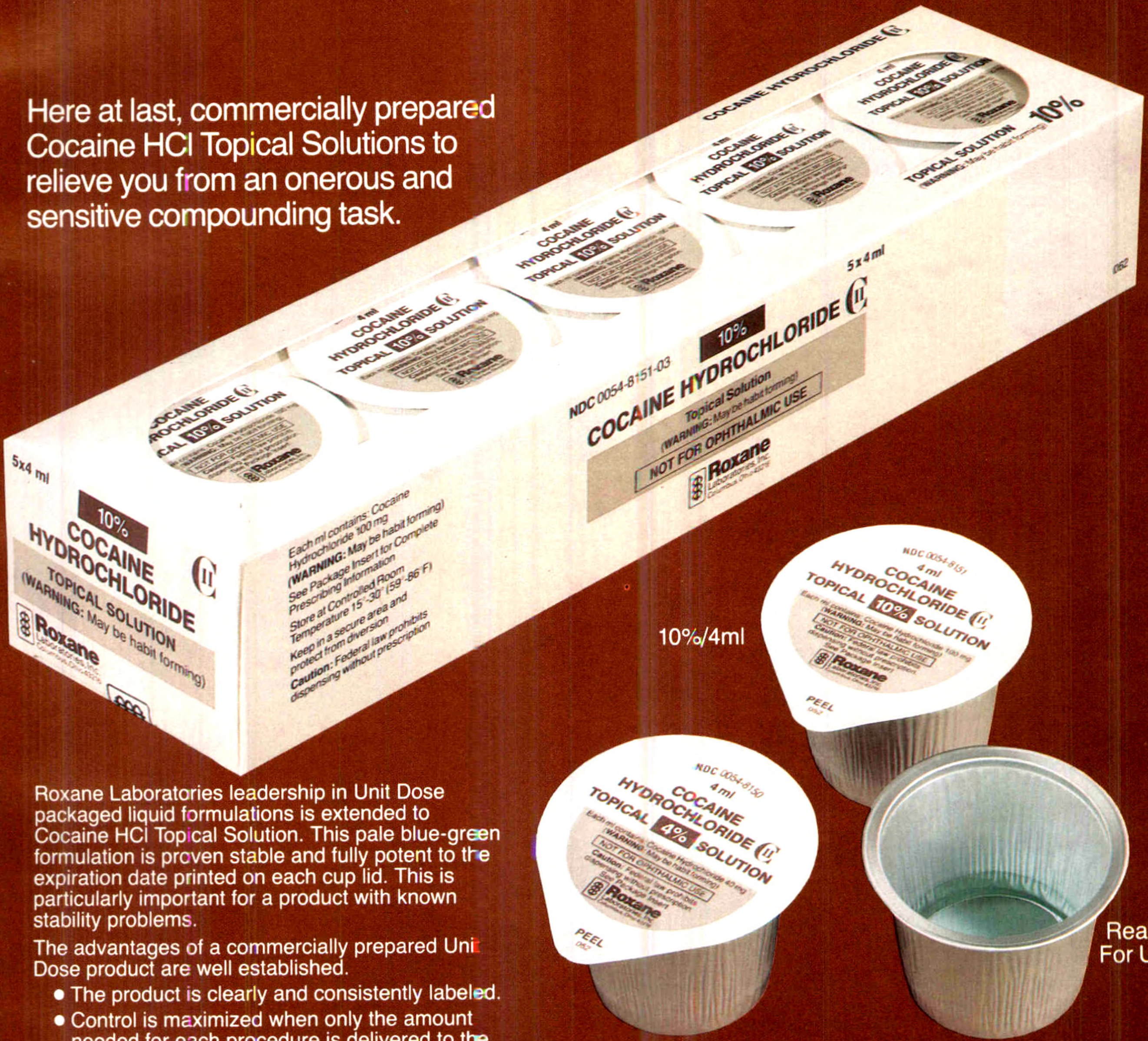

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CONTRAINDICATIONS

Cocaine Hydrochloride is contraindicated in patients with a known history of hypersensitivity to the drug or to the components of the topical solution.

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Carcinogenesis, Mutagenesis: Long-term studies to determine the carcinogenic and mutagenic potential of cocaine are not available.

PRECAUTIONS

The safety and effectiveness of Cocaine Hydrochloride Topical Solution depends on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status.

Cocaine Hydrochloride Topical Solution should be used with caution in patients with severely traumatized mucosa and sepsis in the region of the proposed application. Use with caution in persons with known drug sensitivities.

ADVERSE REACTIONS

Adverse reactions may be due to high plasma levels as a result of excessive and rapid absorption of the drug. Reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

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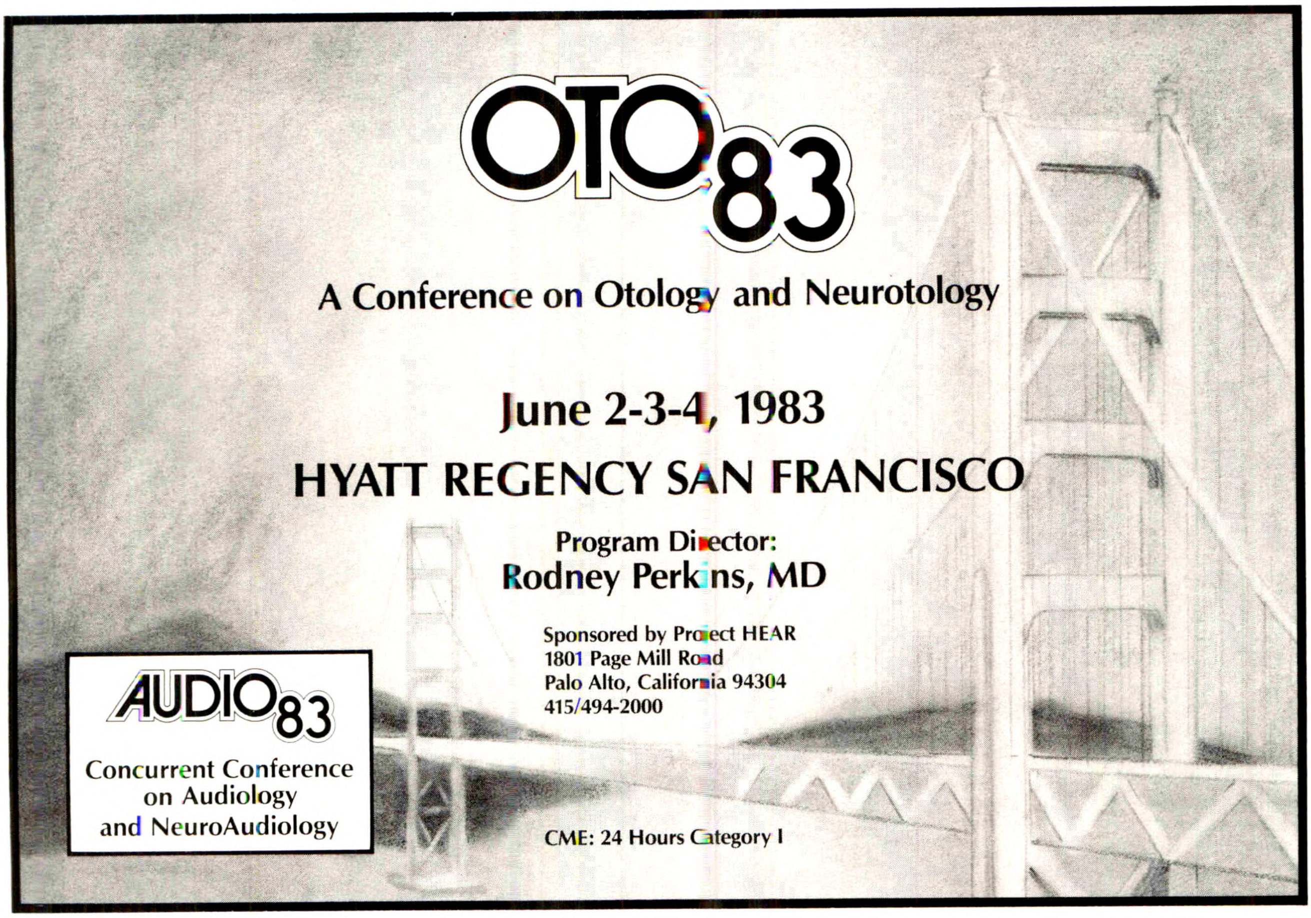

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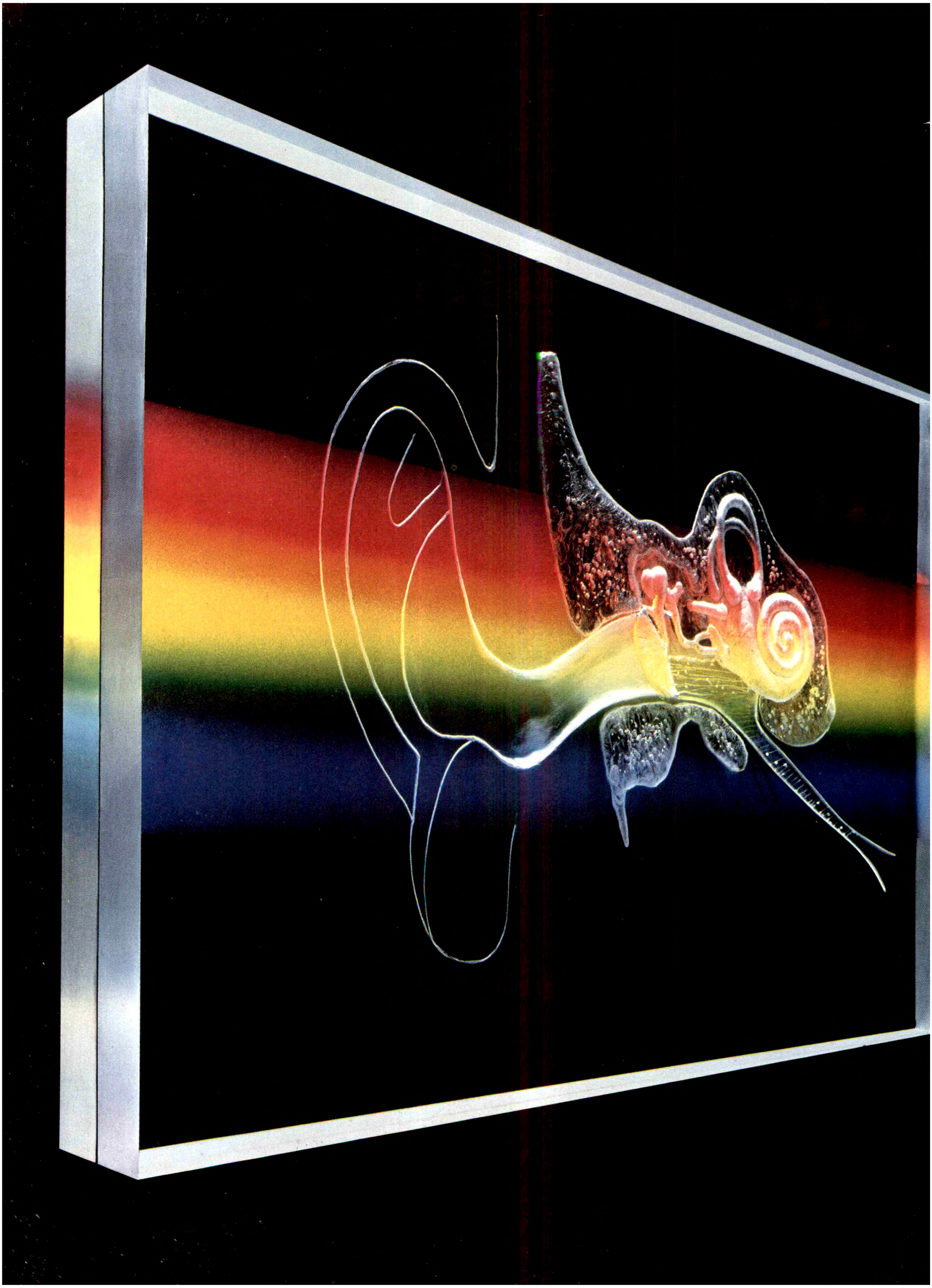

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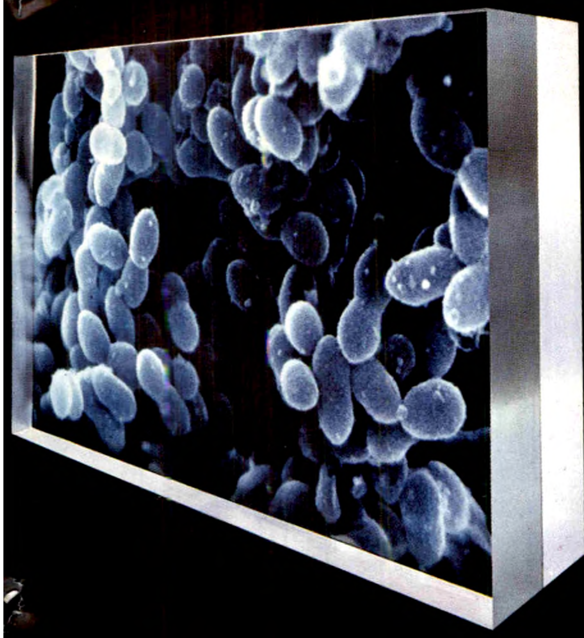

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Ceclor is contraindicated in patients with known allergy to cephalosporins and should be given cautiously to penicillin-allergic patients.

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Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

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Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below:

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [061782O]

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EDITORIAL

The most rapid change in the history of the *Annals* has occurred over the past year. The election of a new editor by the Board of Directors was followed quickly by the appointment of a new managing editor and a new business manager, reconstituting the group that forms the heart of the Annals company. These changes were brought about by two main factors: first, the prescient wish of Ben Senturia to effect a change in the chief stewardship of the *Annals* in a thoughtful and orderly manner, and second, the retirement of the managing editor of many years, Bess Arick So many changes occurring closely together could have posed major operational problems, especially since they were followed so quickly by Ben's death, which saddened us last summer. Even after changing roles from editor to coeditor he continued to have major input into the production process. But his wisdom and planning with the Board of Directors enabled the transition to proceed with hardly a ripple. It has been very heartening to receive telephone calls and letters from a great many individuals offering help in this transition period. I am very appreciative of such support.

The past year marks another signal event — publication of the 100th *Annals* supplement. This format for publication has been extremely successful in meeting the particular needs of many of our authors. It is popular not only because it affords more rapid publication, but also because it gives the author's material a certain dignity which derives from separate identification. We are very proud that the list of supplement authors constitutes a "Who's Who" in the specialty.

I would like to express appreciation to our Board of Editors for the immense contribution they have made to the consistently high quality of the contents of our issues. Ours is an honorary board, but the names on our masthead are not there simply in recognition of the excellence of these persons in our specialty. They are a working board who serve you as readers as they would serve their friends, closely examining, weighing and evaluating manuscripts to insure that only those worthy of your time are offered in the *Annals*. There is no monetary compensation. Often I am embarrassed to realize the amount of time invested by many of our board members in reviewing, suggesting revisions and re-reviewing manuscripts. The rejection rate for materials submitted for publication is approximately 60% for independent papers, and much more time is spent reviewing and detailing the reasons for rejection of a paper than for acceptance. Further, nine of ten papers accepted undergo at least one revision, and it is not unusual for a paper to undergo four. Every revision is reviewed as critically as the original.

I am also deeply indebted to that legion of reviewers not on our editorial board, in this country and throughout the world, whom we have called upon from time to time because of their special expertise.

The year 1983 holds much promise, hope and some real fears. The chief hope is for continued peace among the great nations of the earth despite the buildup of a range of destructive instruments. Our promise for the future is in the scientific leadership nurtured in our public and private institutions and the contribution these physicians and scientists can make to the quality of life throughout the planet. Because the regionalism of journals that emphasize only American papers seems inappropriate in the present shrinking world, the *Annals* will continue to strive to serve the international community of otolaryngologists.

Brian F. McCabe, MD
Editor

Ann Otol Rhinol Laryngol 92:1983

INTERFERON AND LARYNGEAL PAPILLOMATOSIS

THE IOWA EXPERIENCE

BRIAN F. MCCABE, MD KEITH F. CLARK, MD

IOWA CITY, IOWA

Preliminary findings are presented from an ongoing clinical trial of 19 patients with moderate-to-severe respiratory papillomatosis. The patients were treated with partially purified human leukocyte (alpha) interferon; after treatment periods ranging from 6 weeks to 12 months, six had no residual disease, seven had minimal residual disease, four had moderate disease not requiring rescue laryngoscopies, and two had not responded to treatment. No patient had to be removed from the study because of drug toxicity. Although these appear to be among the best results in the literature to date, we do not know how long treatment will be required.

INTRODUCTION

Since Marcellus Donalus[1] reported "warts in the throat" in the 17th century, adjectives such as relentless, proliferative, befuddling, invasive and vexing have been used to describe juvenile laryngeal papillomatosis (JLP). Over 100 years ago MacKenzie[2] differentiated this disease from other laryngeal masses and used the term papilloma. He reported it to be the most common benign tumor of the larynx. Curative treatment continues to be elusive, and the judgment by Clark[3] in 1908 that papillomas will not respond to treatment until their period of active growth has passed may well be appropriate today. Although a myriad of treatments have been tested over the years, children and adults with papillomatosis continue to experience hoarseness, airway obstruction and tracheopulmonary invasion despite frequent operative procedures.

Recently Haglund et al[4] stimulated interest in the possibility of using interferon in treatment of JLP. They described definite response in each of seven patients treated with human leukocyte interferon prepared by the Finnish Red Cross Blood Transfusion Center. However, only two of the patients remained disease-free after interferon treatment was discontinued. Goepfert et al[5] reported 12 patients treated with interferon from the same source, five with complete response but with only two of five sustained; three with good response with one of three sustained; two, moderate response with one of two sustained; and two, slight response, with both sustained. Patient age ranged from 2 to 35 years. The main dose-limiting side effect was SGOT elevation. Again, papilloma proliferation and growth was observed to increase when the interferon dose was reduced in amount or frequency. They considered their experience with that interferon discouraging and discontinued its use. Gobel et al[6] reported the unsuccessful use of human fibroblast interferon in two children in whom they subsequently achieved complete control with human leukocyte interferon.

A variety of synthetic compounds capable of inducing interferon production in vivo has been reported.[7] Leventhal et al[8] described treatment of two children with aggressive JLP involving the tracheobronchial tree. High serum levels of interferon were induced with a synthetic polynucleotide, but the pulmonary course was unaltered and the benefit limited to a reduction in the frequency of operative procedures.

Interferons are polypeptides produced by virtually all eukaryotic cells in response to viral and nonviral stimuli. Classification is based on cell of origin and type of inducer. Type 1 interferons are induced by viruses and include leukocyte (alpha) and fibroblast (beta) interferons, while type 2 includes immune (gamma) interferon which is secreted by lymphocytes following a specific antigenic or mitogenic stimulus.[9] These interferons each have distinct physicochemical properties and clinical effects.

Microquantities of interferon are required for the development of the antiviral state, but the actual mechanism is incompletely understood and thought to involve a complicated sequence of events. Borecky[10] suggested that interferon may act on several viral activities: viral uncoating, transcription of viral genome, viral protein synthesis or virus assembly. He also described antiproliferative and immunoregulatory effects.

Viral presence is thought to be the necessary condition for JLP; however, the evidence to date is indirect. It is assumed that human papilloma virus (HPV) is associated with mucosal papilloma, but HPV has not been reproducibly identified in this lesion. Lack of a successful cell-culture system and inability to isolate the virus have hampered study of the molecular biology and genetics of HPV.[11] HPV is known to be a double-stranded DNA virus with at least five serotypes, each causing tissue-specific infections.[11] Much of the difficulty in proving viral presence may stem from the possibility that HPV ex-

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From the Department of Otolaryngology-Head & Neck Surgery, University of Iowa, Iowa City.

REPRINTS — Brian F. McCabe, MD, Department of Otolaryngology-Head & Neck Surgery, University Hospitals, Iowa City, IA 52242.

TABLE 1. PATIENT PROFILES

Case	Age at Diagnosis (yr)	Rescue Endoscopy Interval (wk)	Papilloma Site	Tracheostomy	Age at Entry (yr)
1	2	1	Larynx	No	3
2	1	3	Larynx	Yes	3.5
3	5	4	Larynx	No	5
4	3	4	Larynx	No	4
5	1	4	Larynx	No	2
6	0.6	4	Larynx, trachea	Yes	2
7	1.5	4	Larynx, trachea	Yes	2
8	2	4	Larynx	No	3
9	0.8	3	Larynx	No	2
10	1.6	2	Larynx,	No	3
11	0.7	8	Trachea	Yes	2.5
12	1	8	Larynx	No	2
13	1	6	Larynx	No	3.5
14	2	4	Larynx, trachea, lung	No	7
15	1	24	Larynx, trachea, lung	Yes	11
16	2	8	Larynx, trachea, lung	No	15
17	12	12	Larynx	No	42
18	1.5	12	Larynx, trachea, lung	Yes	17
19	2	6	Larynx, trachea	Yes	24

ists only in superficial layers of mucosa or epithelium, may incorporate viral DNA into the genome of infected cells, or may exist in a masked or naked form.[12-14] Recent work in molecular biology aimed at confirming viral etiology in this disease has included techniques of nucleic acid hybridization, endonuclease mapping and immunohistochemical analysis.[14-16]

Unequivocal antiviral effects have been demonstrated in animal and human trials using human leukocyte interferon therapy.[17] Antiviral effects can be seen at doses that appear not to result in serious side effects.[18] This report presents experience with human leukocyte interferon treatment in patients with "viral" respiratory papillomatosis.

METHODS

Nineteen patients were entered into a prospective study to examine the efficacy and toxicity of partially purified human leukocyte interferon injected three times per week. Patients with moderately severe to severe histologically proved respiratory papillomatosis were selected. Moderate severity was defined as disease requiring endoscopic removal more frequently than every 3 months *for airway rescue*, or evidence of progression to new anatomic sites. Patients requiring tracheotomy or with tracheal, bronchial or pulmonary involvement were termed severe. Age at entry ranged from 1.5 to 42 years. The procedures and possible side effects were described in detail and informed consent was obtained from each participant prior to entry into the study.

All patients were admitted to the hospital for pretreatment evaluation. Tests included complete blood count with differential, platelet and reticulocyte counts; liver and renal function tests; immunoglobulin quantitation; chest roentgenography and lung tomography as indicated; vital signs with height and weight and direct laryngoscopy with biopsy and photographic tumor mapping. Pretreatment tests were repeated at approximately 1-month intervals. As treatment progressed testing frequency varied according to side effects, dosage and timing of treatment.

Partially purified human leukocyte interferon was purchased from the New York Blood Center, Inc. and stored frozen until use. Intramuscular injections were given three times per week. Initial doses for children were generally 3-million units per injection, while older patients received between 4-million and 10-million units. Family members or patients were taught to ad-

TABLE 2. EFFECTIVENESS OF INTERFERON TREATMENT IN MANAGEMENT OF 19 PATIENTS WITH PAPILLOMATOSIS

	Residual Disease at 6-week Intervals Month of Therapy								
Case	1.5	3	4.5	6	7.5	9	10.5	12	Temporary Side Effects
1	Min		Free		Min		Free	Free	WBC 3,800/μL with 3 million units
2	Min		Free		Free	Min			
3	Free	Free		Min	Free		Min		Thrombocytopenia 50,000/μL with 3 million units
4	Min			Min					
5	Min	Min		Mod	Mod				WBC 4,000/μL at 8 months with 3 million units
6	Mod	Mod	Min						
7		Min		Min					
8	Mod	Mod	Mod	Mod					
9	F	F	F	F					SGOT to >100 IU/L with 3 million units Frequent fever
10	Mod	Min							
11	Free	Free							
12	Free	Free		Free					WBC 3,800/μL with 2 million units
13	Min								
14	Mod								WBC 3,000/μL with 3 million units
15	F	Mod	Mod						WBC 2,900/μL with 5 million units
16	Mod	Min	Mod	Mod	Mod	Mod			WBC 3,200/μL with 5 million units
17	Mod				Free				
18	F	F	F	F					
19	Mod								

Free - No residual disease; Min - Minimal residual disease; Mod - Moderate disease present but no rescue laryngoscopies necessary; F - Failure, no response and rescue laryngoscopies necessary.

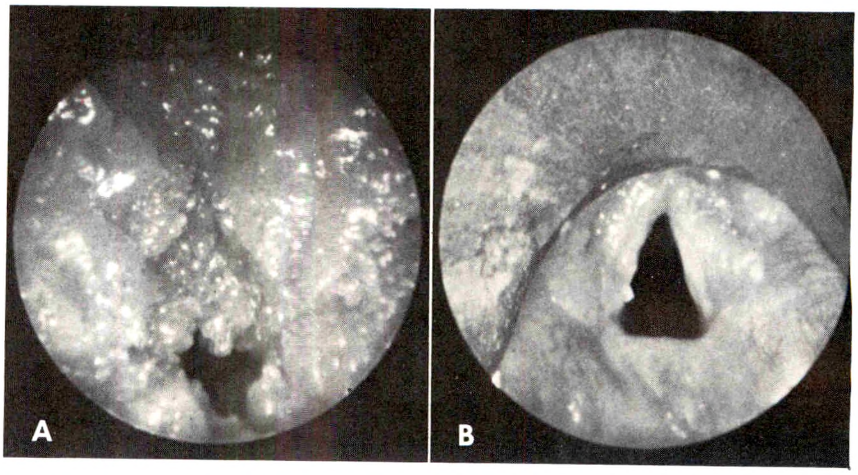

Fig 1. (Case 3) A) Diffuse papillomas with posterior airway before interferon treatment. B) Larynx after 6 weeks' treatment.

minister the drug and did so at home in most cases. Follow-up endoscopy was performed approximately 2 weeks after entry into the study and routinely thereafter every 6 to 12 weeks. Biopsy and photographic and diagrammatic documentation were done prior to CO_2 laser and/or microsurgical reduction of the lesions. *No attempt was made to eliminate all lesions* but only to establish an airway or to reduce the antigenic tumor load.

The protocol we established specified a decrease in dose of one third every 3 months until a maintenance dose of one third the pretreatment dose is reached. All patients receive treatment for 1 year. One patient has reached that point, and treatment has been stopped. Higher dosage levels and/or constant levels are used in adult patients or patients with residual disease. Interferon is stopped temporarily (usually 1 week) if the WBC drops below 4,000/μL, platelets below 75,000/μL or SGOT is above 100 IU/L. Interferon treatment resumes when values return to normal or at least to near normal. Treatment is interrupted when constitutional symptoms are not controlled by Tylenol. Persistent toxicity requires dose reduction. In no patient has toxicity required cessation of treatment.

From November 1981 to November 1982, 13 children under 6 years old, two aged 6-14, and four over 14 years old received interferon treatment (Table 1). Treatment periods ranged from 6 weeks for the newest patient to 12 months for the oldest. All patients received three injections per week and dose level varied from 1 million to 10 million units. None of the patients under 6 years old received more than 4 million units per dose. The single patient who was not treated with CO_2 laser excision received ultrasound therapy before entry into the study. Seven patients received preinterferon (solely surgical) management at this institution and the remainder were referred from other parts of the country.

RESULTS

Six of the 19 patients were papilloma-free at some point during the study (Table 2 and Figs 1 and 2). Of these, three were treated over a 9-month period and underwent dose reductions to 1 million units. Two of the six had papilloma regrowth and subsequent dose elevation. One patient could not tolerate 3 million units because of polymyalgia and arthralgia but tolerated 1 million units well with only minimal residual disease after 8 months. After treatment seven patients had minimal residual disease, and four had moderate residual disease but not sufficient to require rescue laryngoscopies. Two patients were failures despite a constant dosage level.

Seven patients had minimal-to-moderate persistent disease and were maintained on initial or elevated dosages for more than 4 months.

Eight of the 19 study patients had tracheal papillomatosis. Five showed improvement of their tracheal disease after treatment and two were decannulated (Fig 3). Of the four cases with pulmonary papillomatosis, two (14 and 16) showed radiographic evidence of improvement.

No evidence of significant toxicity was observed

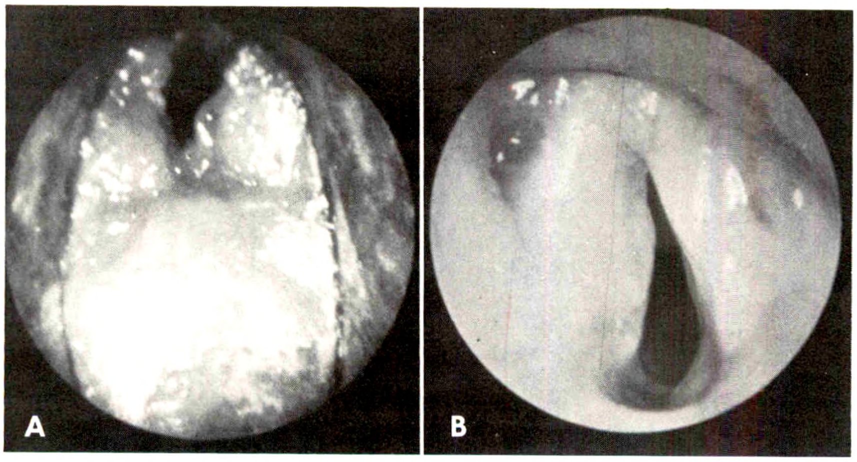

Fig 2. (Case 4) A) Papillomas along true vocal cords before interferon treatment. B) True cords after 2 months' treatment.

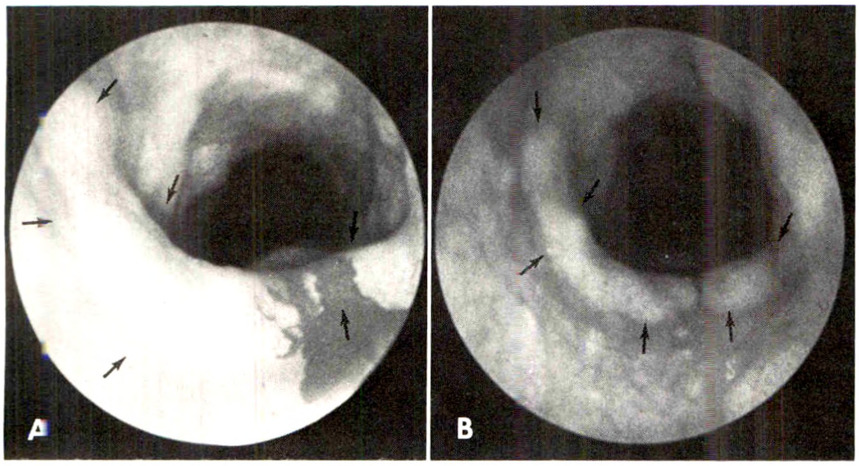

Fig 3. (Case 16) Tracheal papillomas (arrows). A) After 3 weeks' interferon treatment. B) After 3 months' treatment.

in this study. Most patients had the expected reactions of fever, chills, anorexia and occasional vomiting during the first 2 weeks of treatment. These side effects were dose-related and resolved within 48 hours after injection. Each subsequent injection was associated with fewer systemic reactions, and Tylenol was helpful in preventing reactions.

Many patients experienced sporadic, transient temperature elevations throughout treatment and several of the younger patients routinely had temperature fluctuations on the day of injection. One patient had a seizure 24 hours after injection; this patient was febrile (40.5C) from an upper respiratory infection but did not have a history of febrile seizures. There was no significant correlation between extent and severity of side effects and regression of papillomas. Several patients had mild erythema and induration at the site of injection early in the course of treatment, but there were no serious injection-site reactions. No significant growth disturbance, weight loss, renal toxicity, alopecia or altered susceptibility to infection were observed.

In six patients the WBC dropped below 4,000/μL but returned to normal after withholding interferon for 1 week. Two patients experienced a second transient bout.

One patient had thrombocytopenia on several occasions which resolved each time after a 1-week rest from interferon. This patient had a pretreatment platelet count of 123,000/μL which dropped on three occasions to the 50,000 to 75,000 range without symptoms or signs of bleeding. The patient was tapered to 1 million units and has had no further thrombocytopenia below 100,000/μL.

Serious elevation of liver function tests was not observed. Most of the children under 15 years old had SGOT results of approximately 60 IU/L. None of the older patients experienced elevation of liver function tests. One patient had SGOT elevation to around 150 IU/L after maintenance for 6 months on 3 million units of interferon. This occurred while the patient was receiving doses of 3 million units and undergoing general anesthesia weekly in the treatment of laryngeal stenosis. Liver enzymes consistently rose on the day general anesthesia was administered and fell between operations, independently of dosage modification. Over a 2-month period with doses of 2 million units, this problem resolved. Hepatitis screening was negative and bilirubin level normal.

DISCUSSION

Juvenile laryngeal papillomatosis can be an aggressive and tenacious disease involving significant morbidity and economic cost. Majoros et al[19] reviewed a large series of patients treated with microsurgical removal of papillomas in 1964. None of the patients with disease beginning during the first 7 years of life had remission in less than 3 years, and the average duration of disease was over 12 years. Today treatment with repeated hospitalizations for laryngoscopic removal would require expenditures of many thousands of dollars over 12 years; costs the first 3 years, assuming four admissions per year at approximately $3,000 per admission, would be well over $30,000. Some of our patients required more than 12 admissions in just 1 year, incurring an *annual* cost of over $30,000. Strong et al[20] presented a review of patients treated with CO_2 laser ablation. Only three of 18 patients with tracheobronchial tree disease had remission after repeated operations over an apparent 3-year period. The authors suggest that something more than total ablation is needed before papillomas can be eradicated consistently and permanently.

Considering the natural history of JLP, its presumed viral etiology, and the variety of treatments that have failed to cure it, further clinical trials with interferons are justified. Basic scientific knowledge about interferon has expanded considerably since Isaacs and Lindenmann[21] first discovered it in 1957. Numerous therapeutic models have shown that interferon modulates viral infec-

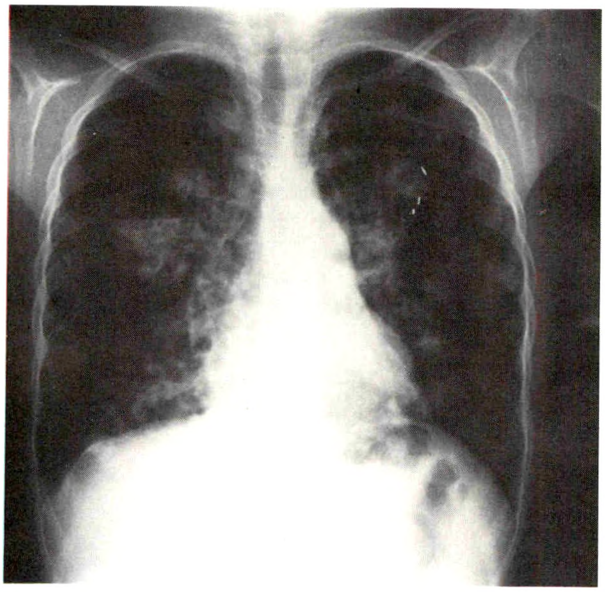

Fig 4. (Case 14) X-ray film showing severe cavitary pulmonary papillomatosis.

tions. Although it has been well established that virtually all viruses are susceptible to the activity of interferon, the underlying mechanisms are only vaguely understood.

The leukocyte interferon used in this study was purchased from the New York Blood Center (NYBC). It is pooled from buffy coat lymphocytes and is approximately 1% pure. This preparation is similar to that produced by the Finnish Red Cross Blood Transfusion Center. Both alpha interferons have at least four distinct subtypes of interferon activity. Highly pure DNA-recombinant and lymphoblastoid interferon may prove useful in the treatment of JLP as data from clinical trials are collected. This remains to be seen. Purity of interferon preparations may have an influence on both response and side effects. NYBC is currently preparing a highly purified alpha interferon that may be released for clinical trials soon.

Results of the present study are consistent with those reported by Haglund et al[4] and Goepfert et al,[5] but seem to be a little more encouraging. We need more experience to say more. We identified a primary group of sensitive patients who responded readily during the early stages of interferon treatment. A secondary group benefited but had some persistent disease despite continued full-dose treatment with interferon. This is an interesting group — would a different interferon have achieved better results? We are in the process of pursuing this alternative. We also identified a small group of patients who seem to be poor responders. Differences cannot be explained on the basis of disease site or duration before treatment. There seems to be no relationship between response and level of toxicity or side effects. The only correlation was with age, ie, the most dramatic responders were children in the youngest age group.

Toxicity was mild, transient and dose-dependent; although all patients experienced some, no patients were removed from the study because of drug-related toxicity.

The main dose-limiting side effect reported by Goepfert et al,[5] SGOT elevation, was not seen in this study. The major differences between the two studies are frequency of administration and source of interferon. They generally used higher doses more frequently (on a daily basis) with adults and slightly lower doses with children. Appropriate frequency and dose level as well as type of interferon thus seem important to us.

Early response of pulmonary papillomatosis to interferon has been documented in two cases (14 to 16). This seems to us particularly important in this study. It is hard to make much of just two cases, however. In cases 14 and 15 the lung lesions fluctuated in size prior to treatment, making assessment of the effect of interferon difficult. Pulmonary papillomatosis (Fig 4) is particularly troublesome because mortality in JLP, aside from that related to operative incident or acute airway destruction, is caused by destruction of pulmonary tissue which radical efforts, including pneumonectomy, seem unable to contain.

The most troublesome finding is regrowth of papillomas after interferon treatment has been stopped. This phenomenon has been observed by others.[4,5] Goepfert et al[5] reported breakthrough growth after 4 to 7 months of interferon treatment. Our experience is still ongoing, but we have seen regrowth after dropping the dosage level in two patients who were dramatic responders initially (cases 2 and 3).

Our data indicate that partially purified human leukocyte interferon from NYBC is safe and effective in many patients with JLP. Data also indicate that many children are spared a long sequence of rescue laryngoscopies involving hospitalizations, trips to the operating room with the attendant mortality risk of a tiny airway already seriously compromised, and, it should be added, strain on the coronary arteries of a very worried laryngeal surgeon.

FINAL COMMENT

We should note that the nearly 500 laser laryngoscopies performed in this study (Table 1) and on other patients in this institution have given us a healthy respect for the potential damage that the laser can do to small larynges. Anterior commissure webs and posterior interarytenoid scarring compromising abduction have been a significant problem in some patients. We believe this to be the result of the laser, which can produce scar contracture we did not see in the days of removal by forceps. We urge laser users to consider avoiding the commissures, and in other areas to de-bulk rather than seek total extirpations of visible papillomas.

REFERENCES

1. Donalus M, quoted by Webb WW. Papillomata of the larynx. Laryngoscope 1956; 66:871-918.

2. MacKenzie M. Essays on growths in the larynx with reports of an analysis of one hundred consecutive cases treated by the author. Philadelphia: Lindsay and Blakiston, 1871.

3. Clark JP. Papilloma of the larynx in children: a further consideration of the subject. Trans Am Laryngol Assoc 1908; 283.

4. Haglund S, Lundquist P, Cantell K, Strander H. Interferon therapy in juvenile laryngeal papillomatosis. Arch Otolaryngol 1981; 107:327-32.

5. Goepfert H, Gutterman J, Dichtel W, Sessions R, Cangir A, Sulek M. Leukocyte interferon in patients with juvenile laryngeal papillomatosis. Ann Otol Rhinol Laryngol 1982; 91:431-6.

6. Gobel U, Arnold W, Wahn V, Freuner J, Jurgens H, Cantell K. Comparison of human fibroblast and leukocyte interferon in the treatment of severe laryngeal papillomatosis in children. Eur J Pediatr 1981; 137:175-6.

7. Field A, Fytell A, Lampson G, Hillernan M. Inducers of interferon and host resistance. II. Multistranded synthetic polymieleotide complexes. Biochemistry 1967; 58:1004-9.

8. Leventhal B, Kashima H, Levine A, Levy H. Treatment of recurrent laryngeal papillomatosis with an artificial interferon inducer (poly IC-LC). J Pediatr 1981; 99:614-6.

9. Friedman R. Antiviral activity of interferons. Bacteriol Rev 1977; 41:543-67.

10. Borecky L. Twenty years after the discovery of interferon: the progress and the persistent problems. Acta Biol Med Ger 1979; 38:709-31.

11. Faras A, Krzyzek R, Ostrow R, et al. Genetic variation among papilloma viruses. Ann NY Acad Sci 1980; 354:60-70.

12. Boyle W, McCoy E, Fogarty W. Electron microscopic identification of virus-like particles in laryngeal papilloma. Ann Otol Rhinol Laryngol 1971; 80:693-8.

13. Farfeed G, Davoli D. Molecular biology of papovaviruses. Ann Rev Biochem 1977; 46:41-52.

14. Zuick C, Krzyzek R, Watts S, Faras A. Relationship between condylomata and laryngeal papillomata. Ann Otol Rhinol Laryngol 1980; 89:467-71.

15. Coggin J. Workshop on papilloma viruses and cancer. Cancer Res 1979; 39:545-6.

16. Lack E, Jenson A, Smith H, Healy G, Pan F. Immunoperoxidase localization of human papilloma virus in laryngeal papilloma. Intervirology 1980; 14:148-54.

17. Krim M. Towards tumor therapy with interferons. I. Interferons: production and properties. Blood 1980; 55:711-21.

18. Merigan T. Pharmacokinetics and side effects of interferon in man. Tex Rep Biol Med 1977; 35:541-7.

19. Majoros M, Parkill E, Divine K. Papilloma of the larynx in children: a clinicopathologic study. Am J Surg 1964; 108:470-5.

20. Strong M, Vaughan C. Cooperband S, Healy G. Clemente M. Recurrent respiratory papillomatosis: management with the CO_2 laser. Ann Otol Rhinol Laryngol 1976; 85:508-16.

21. Isaacs A, Lindenmann J. Virus interference. I. The interferon. Proc Soc Lond [Biol] 1957; 197:258-67.

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SATELLITE SYMPOSIUM ON PEDIATRIC OTOLARYNGOLOGY

A Satellite Symposium on Pediatric Otolaryngology will be held October 17, 1983, in Tokyo. For further information, contact Keijiro Koga, Department of Otolaryngology, National Children's Hospital, 3-35-31, Taishido Satagayaku, Tokyo, Japan.

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PSYCHOLOGICAL PROBLEMS OF THE DEAF

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Although hearing is known to play a major role in the psychological development of human beings and their interactions in the society and culture, very little research on the effects of hearing loss on the psyche and its development has been undertaken. This paper discusses the problems of deafness as they impinge upon personality, its development and social adjustment, acquisition of language, and parenting. The physician's role as it relates to the deaf patient and to the parents is described.

INTRODUCTION

The greatest handicap of deafness lies in the fact that it leads to loneliness, introversion and unsociability by separating a deaf person from others with normal hearing through lack of the optimal pathways of communication. Early deafness occurs at the time in life when perhaps the most important stimulus a child receives — the sound of the human voice — is absent. Without this stimulus the child may go through life without making significant contact with the society and culture into which he or she was born. From medieval times to the present, this fate has not been, and still is not, uncommon in a great part of the world.

Reactions to deafness by the hearing world have not changed fundamentally over time. It seems remarkable that some forms of disability make a deep impression on us, while other handicaps appear to have little effect. Not so long ago people went to the madhouse to enjoy themselves, looking at the funny gestures of the patients, listening to their muddled talk and even arousing them to excitement in order to hear bad language and invective. In those days, the position of the deaf was especially difficult because they were thought to be "possessed by the devil" or, at least, morally deficient. The deaf could not obtain "the true faith" since in the Holy Scriptures is written *fides ex auditu* (faith comes from hearing).

In this century we are not totally free from such attitudes. When I was a boy, children wearing spectacles ran the risk of being hooted after. Today, laughing at a blind man, a cripple, or a severely retarded person is unacceptable; but these are highly visible disabilities. In instances where the handicap is not as immediately and grossly obvious, our compassion and our delicacy are all too often absent. To laugh at an inappropriate response given by a deaf person who has misunderstood the question or the context is not uncommon. Jokes about poor hearing are generally regarded as humorous and acceptable, when, in fact, they reflect extremely limited sensitivity to the needs of this group of handicapped.

Bertolt Brecht reminds us in *The Threepenny Opera*, "Those who are in the light can be seen, but one does not see those who are in the dark." I shall try to bring the deaf person somewhat more into the light.

DEAFNESS: EXTENT AND NATURE OF THE DISABILITY

The implications of deafness for personality development and life-style are very complex and not well understood. However, because some degree of hearing loss is commonly experienced with aging, all of us come into contact with this problem, some on a regular basis. The need for understanding and a degree of empathy is, thus, widespread. While it is not possible to discuss the problem in a complete and definitive manner, it is my purpose to highlight particular aspects of profound deafness as they relate to the quality of life.

Deafness is a very serious disability. In nature, a blind animal can exist (witness the mole that is blind and the kiwi that is nearly blind), but among vertebrates those born deaf are *never* able to survive; even those losing their hearing later very rarely survive, even if they live in a herd. Deaf animals do not live because hearing is the organ of warning, a sense that never sleeps and is always vigilant. Hearing warns the hunted and points the way for the hunter, thus providing both with a chance for survival. For human beings, the warning function is perhaps not so critical as it is for a rabbit or even a lion. Nevertheless it's important. Imagine the appalling sensation when suddenly someone stands before you, without your having prior clues to his presence. This "someone" easily could be a fast motorcycle or car. Or, visualize your small, noisy son suddenly jumping upon your knees without your having noticed his approach. This kind of imaging can perhaps help us understand better one of the psychological difficulties a deaf person must endure.

Functions of Hearing in Human Beings. The sense of hearing enables human beings to establish

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contact with others through language. It makes humans social beings, able to speak, to express themselves and to think.

As an organ of warning and of contact with others, hearing is extremely important, but there is still more to it. Hearing is the sense that keeps us in contact with life itself. The rhythm of life is thus manifested to us: even in complete silence we hear our heart beat, we perceive the flow of blood through our vessels, we listen to the activity of our intestines or to the contractions of our muscles. Our bond with our noisily living bodies is so strong that the sudden loss of hearing must have tremendous impact. Persons have reported the sensation that one "loses contact with life" and "feels oneself dead among the living," or "walks about like a dead man." These are characteristic expressions concomitant with sudden hearing loss.

Suicide rates are also higher among those who have suddenly become deaf than in the general population. In wartime, the highest incidence of suicides was found among the wounded with sudden deafness and not, as one might presume, among the severely mutilated.

The sense of hearing is of great significance for the normal existence of the individual both with respect to social interactions and to personal life. This is perhaps nowhere more evident than in the small talk, the standard openings and closings of everyday interactions. We greet each other and indicate availability, openness, interest, concern, assent, dissent, and needs with trivial kinds of utterances which convey meaning but which, in many instances, we regard as not worth the effort of saying more than once. We do not enjoy repeating unimportant things, yet human relationships depend in part on such interaction.

Absence of Compensatory Senses. Sight and hearing are the two main pathways by which impressions from the outer world reach the mind. If sight fails, the blind can receive some benefit from the sharpening of their hearing, which is helpful in adapting to a dark world. For the deaf, however, the sense of sight cannot function above the normal level. Sight is directed by hearing. Without sound stimuli, visual capacity is reduced. The sight of deaf people is not sharpened, but blunted. In a group, a deaf person is unable immediately to read the lips of the person speaking because there is no way to know where to look.

Oppressive Qualities of Deafness. Most people do not understand the importance of deafness because it cannot readily be imagined. Anyone can experience the disability of blindness simply by walking out of doors on a very dark night, or by closing his or her eyelids. But no one can become temporarily deaf, and nature does not provide "earlids." Moreover, in modern life, many people are annoyed by noise and seem to yearn for silence, but it is not the total silence experienced by the deaf that is sought.

What is it that makes quietness so dear to us? In describing silence the poet refers to sounds: a breath of wind whispering in the treetops, a murmuring brooklet, the breaking of a twig. Why is silence so restful, so soothing? Because relative silence enables us to perceive distant sounds, it creates a feeling of infinite space: a church clock chiming miles away or the evening cry of a distant bird. The world is vast, but because we rarely experience it with our senses, we very deeply enjoy the feeling of belonging to it, though we usually do not realize that this joy is caused by "hearing silence."

The oppressive thing about loud noises is that they give us the feeling that the world is crashing in on us. In a knitting mill, near a jet plane, or in a boilermaker's workshop, the world is no greater than what is enclosed in the raging noise. Similarly, in the silence of deafness no vital space is present, no feeling of freedom. Instead, silence for the deaf is oppressive and encompassing. It is not the silence valued by those with normal hearing which enables them to experience a widening of their vital space and a feeling of relatedness to the universe.

A few years ago, one of the terrors of space travel was believed to be the soundlessness of outer space. A journalist describes his feelings after being in an echoless room: "In a lugubrious room, made unpenetrable to sound on all sides, completely soundproof, I experienced what the silence of space might mean. This complete absence of sound is an unbelievable terror. One can bear it as some new experience while your friends are waiting outside the door of the laboratory to open it, as soon as you call them, but I did not need very much imaginative power to realize that such an inhuman, ghastly, dead silence could eventually lead to despair, a hysterical and disastrous despair, if one had to endure it in the perfect solitude of space" (personal communication). I might add, ". . . or in the solitude that surrounds a deaf person." The deaf person differs from the journalist in a crucial way: he cannot open the door of the soundproof laboratory and come out into the hearing world.

DEVELOPMENT OF LANGUAGE

Language development in a normal child involves a sequence of events that starts at birth from all kinds of sensory communication with the mother. The instinctive behavior of the mother (who needs not be the natural mother) while nursing and soothing the child by talking enables the child gradually to acquire mastery of the language of the environment. The child learns the mother's tongue in her lap.

It will be clear that the situation of a deaf child makes this normal procedure of language development impossible. In the normal child, hearing is active from the start. The steps and the voice of the mother announce a dry diaper; jingling cups and plates predict food; and the funny cries of enraptured father, grandmothers, and other relatives bring agreeable sensations of being held and fondled. Since most of these sounds have a pleasant association, baby's attention is attracted more and more. He or she does not merely hear and show some auditory reflex movements, but starts to listen and to trace the source of the sounds.

At the age of three months, a child responds to the human voice, or speech. A baby copies, it seems, the mother, echoing her voice as well as her smile. In this jabbering phase, the ear as the steering element, and in the cybernetic sense, is of paramount importance. The jabbering sounds begin to take on the pitch, rhythm and timbre of the speaking world. Children "jabber" in French, Dutch, Chinese or Russian long before they start to use one word of the language. It is fascinating to observe how, in the second year of life, many children use strings of word-like sounds that strikingly resemble phrases their parents use and that are combined into sentences with the same rhythm and inflections of the language of adults. Though pseudosentences have no meaning, their value is enormous. By imitating verbal and linguistic patterns, the child develops the ability to communicate and make contact with others in an adult manner.

At about six months old, babies start experimenting with the sounds they are uttering, and develop their own baby speech, constantly controlling it through hearing.

At about one year old, children know the rhythm and melody of a language, and thus are able to begin to use words. They name important objects like ball, doll and milk, and some actions like eat, drink and sleep. They internalize such words according to the norms for these symbols in their culture. Vocabulary is extended by listening, talking and listening, making mistakes and listening, correcting mistakes and listening. In this reciprocity and feedback enabled by hearing, children are able to gather a stock of words which later can be linked together in simple sentences. In this manner, children acquire that typically human gift, expressive language, which is the means of communication with others, and is the basis of future intellectual capacity and the ability to engage in abstract thought.

In the deaf child, language development does not take place in this way. The deaf baby in the cradle does not have the opportunity to attach value to the sounds of the environment since no sounds are experienced. The deaf child is secluded from the surrounding living word.

PERSONALITY DEVELOPMENT AND SOCIAL ADJUSTMENT

It is generally recognized that a concept of selfhood begins to develop during the second and third years of life, and is closely tied to language development and training. To what extent are personality development and social adjustment affected by deafness? It can be said that most deaf persons grow up in a restricted environment and, since they cannot communicate properly, they are in great danger of developing more personality disorders and less adequate adjustment than hearing children.

Loneliness is a symptom seen in the deaf child at an early age and also in the severely hard-of-hearing. In interaction between brothers and sisters, the child with defective hearing stands alone. Friendly as well as angry sounds pass by unnoticed. The child learns to assess moods with difficulty. No word-pictures are found for things being observed with the eyes and, since our thinking, particularly with regard to abstraction, *is* word-thinking, the child probably becomes mentally retarded. Deaf children become intellectually starved by lack of concepts. When other children start playing, the deaf do not understand the object of the game. Children lack tolerance and the deaf child may be cast out as an undesired element. Although cruel in nature, such a reaction may be understood psychologically as a defensive response against those who do not completely fit into the group.

No Characteristic Deaf Psyche. Deaf children react according to their individual dispositions. They may withdraw or react aggressively with bursts of temper or underhand tricks, just as normal children with hearing would do in similar circumstances. There are no particular personality traits attributable to deafness. In any random group of children, some are quiet and some tempermental, some aggressive and some gentle, and some stupid and some intelligent.

It should be noted that among people with hearing loss, totally deaf children manifest fewer psychic difficulties than the partially deaf (the hard-of-hearing). Congenitally deaf persons make fewer demands on themselves and others have fewer requirements. For those with less profound hearing loss, the inability to hear properly is a constantly felt shortcoming that tends to foster psychological complications. Deaf people, including children, are not normal persons who lack only one function. They are human beings whose relations with the world around them have been changed fundamentally by the absence of a sense organ essential for meaningful communication. A deaf person is not simply one who has a diminished capacity to hear and interpret sounds, but a developing human being experiencing serious disturbances at the root of his or her being. The deaf person is an individual who reacts normally to a very abnormal set of circumstances.

A hearing child hears mother coming and going. Life does not stop the moment mother goes away from the cradle, as it does for the deaf child. It does not stop each time visual and tactile stimuli fail to reach the child. Because footsteps, voices humming and thousands of other sounds from house and street do not exist for the deaf child, he or she remains alone, separated from the world, until the next time the solitude is broken.

When stimuli *are* received, moreover, they come without any of the auditory warnings which caution the normal child that something is going to happen. Hence, the deaf child is submitted to startling surprises many times a day. The rhythm of life of the deaf child is strongly influenced by the abruptness with which stimuli impinge upon him. Therefore life itself, in the case of a deaf child, is disrupted. It "stops" any time visual and tactile stimuli do not reach the child in the semidark, warm and soft cradle. No sound disturbs the silence, and the child remains alone, separated from the world until the next time the solitude is broken by stimuli abruptly reaching the other senses.

Adjustment and personality problems of the deaf child, to whatever extent they exist, probably reflect primarily normal reactions to the particular circumstances. "In view of the fact that the mental picture of the world in a person's mind is built up of our sense impressions from the outer world reaching the mind of the individual and that all the communication with the outer world is maintained by a constant flow of sense impressions, it is clear that any defect of this source of information must find its counterpart in the mental or physical condition of the individual."[1]

Sir Alexander Ewing stated, "A fear of isolation appears to lie in the minds of many deaf patients. It is inevitable that he should withdraw from social affairs and begin to avoid people. He may then spend too much time alone and brood about his trouble. His interests become narrowed: repressed social tendencies may cause bitterness and suspicion to flood his mind."[2]

Differences in Cases of Congenital vs Acquired Deafness. Psychological reactions probably are more acute in persons who become deaf later in life than in the congenitally deaf who have not learned to master language. Those who lose their hearing at a later stage, after having learned language, can take part in the mental life of their time and their surroundings. Children so profoundly deaf that normal development of speech is not possible are more easily discovered than children who are hard-of-hearing. The latter can acquire some speech but do not adequately hear all the utterances and questions of parents and others. Therefore, they are often thought to be disobedient and difficult. Many things in daily life may escape them and, therefore, they are called dreamers. In school, because they are not able to follow the lessons, they may be taken to be stupid or mentally defective. Expulsion from a circle of friends may lead to fits of temper. The mental and psychological reactions are often stronger in the hard-of-hearing person than in the totally deaf person because the mental development of the latter stops at a more primitive level. Thus, damage to the less primitive and, therefore, more vulnerable psyche of the hard-of-hearing may be deeper and more resistant.

It must be reiterated that various reactions due to hearing deficiencies often may not be recognized as such. What might be mistaken for mental aberration or lack of intelligence is in reality rather often the consequence of a hearing disorder. As soon as the cause is ascertained and education is focused on the underlying disability, such children are very often seen to flourish as if by magic. The retarded boy appears to have normal brains, the aggressive lad is a kind boy who demands a lot of understanding, the dreaming girl proves to be studious indeed. Psychiatric treatment is often unnecessary if the basic cause is discovered and the child is treated correctly by his family and his teachers.

NEEDS OF PARENTS

Parents tend to think of their child not only as a human being but also as an extension of themselves. Their self-esteem is embodied in their child.[3] It is a very traumatizing experience to find that this part of themselves is not normal, but handicapped. The reaction of a mother to the birth of a mongoloid child is very well expressed by Pearl Buck,[4] who describes her own confusion and uncertainty. She required a long time before she was able to accept the sad fact and think constructively about what she needed to do in order to help her child grow and develop.

Providing the kind of atmosphere and environment in which development can occur is a problem for parents of deaf children. The problem is not with the parents' intentions or motives, but rather with the conflicting guilt, denial, and ambivalence which they feel and with which they must deal.

Acceptance. To feel close to a child that is different from the parents and their background of experiences is difficult. The problem of accepting deafness in an offspring is manifested in a variety of ways. Clues abound, but may be easily ignored if a well-meaning friend notes that the child is only absorbed in his play and, therefore, does not hear the mother calling, or is so busy with his hands that he has no time to learn how to talk. Because parents so desperately want the child to have hearing, explanations of seemingly contradictory phenomena and behavior do not penetrate their consciousness. To reports of, "We have seen so often that he looks up when a plane flies over our garden or when we shut the door," the explanation that the child is responding to vibrations rather than hearing sound must be patiently repeated. When the fact that the child does not hear well finally is accepted, it is still a big step to go to the doctor. Often, people are afraid to have their own suspicions confirmed by the findings and statements of medical science. And as soon as they have obtained a medical opinion, they may try to relieve their unhappiness by going to a variety of experts, hoping to be told that the deafness will become less serious as the child grows up, and thus evading responsibility for the necessary steps for the child's development.

Stance Toward Child. Once the decision is made, it is important to understand what it means for parents to send a young child to a special school, very often in another town, under the care of strangers in an institution or in a foster home. After they have finally agreed to give their child to the experts, it is very difficult to leave things entirely in the experts' hands. They hear about other children wearing a hearing aid, or even two; they learn of children with hearing losses who change from a school for the deaf to a school for the hard-of-hearing, or even to the school for normal students, and cannot bear to see their own child deprived of these advantages. They seek advice from others because they want to do everything possible for their handicapped offspring. Not only other doctors, other psychologists, and other teachers, but quacks as well are visited, persons who are quite irresponsible and incorrigible and may promise the most miraculous results, outcomes which responsible experts can never promise.

Professional Support. Failure of quack treatment may have very sad consequences for both the parents and the child, causing deep feelings of guilt. Professionals can be helpful in steering parents toward more useful and productive approaches to the problem of helping the child. *Often, it is an extremely difficult task for the doctor, the psychologist, and the teacher, who know that they are doing everything within their power to treat the deaf child in the best way, to bear the lack of confidence expressed by some parents.* Nevertheless, these professionals must seek to understand the feelings of frustration and irresolution of the parents, who are suffering, and not allow themselves to get angry with them. The child is and remains the child of his parents, and by helping or treating the psychological difficulties of the parents, the child is aided. The time needed for parents to accept their child's handicap and adapt themselves to planning for his or her needs varies greatly. The process has its ups and downs which need to be followed and monitored; inadequate and piecemeal advice is not useful. Sympathy, understanding and the patience to listen and repeat the same informative arguments many times are necessary. These are not small demands on devoted consultants and teachers who regularly must practice a lot of patience in handling deaf pupils. It is not a small task, but a necessary one.

Professionals can also help the parents understand the child's needs vis-a-vis inappropriate patterns of discipline or personal relationships that they may observe or see developing. It is easy to spoil any child, but his or her needs are best served by discipline and self control based on meaningful communication. If love and sympathy seem to be lacking, the physician can help to objectify the parents' attitudes and behaviors. Everything that the health care professional can do to enhance family relationships is beneficial for the growth and development of the deaf child.

SUMMARY

The small deaf child sees people moving their lips and faces and is aware that something is taking place, but does not know what it is. The child watches people respond to each other but can't comprehend how or whether messages pass between them or what sets them on a course of action or directs their behavior. Family members try to include the child in their own circle, but they can't adequately break through the barrier of soundlessness. The deaf child lives through the motions and activity of life without fully comprehending meaning. Meaning comes with verbal language. The generic problem of profound early deafness is not speech but language, as it is used by hearing people.

In discussing some of the implications of deafness for psychological development, I hope that I have made it clear that, for those of us who treat deaf or hard-of-hearing children, knowledge of the anatomy and physiology of the ear, audiograms, hearing aids, and many other very exact data are of paramount importance but not sufficient for achieving optimal growth and development of the child. Understanding the psyche of the deaf child, as well as that of the parents, is necessary, together with a great deal of compassion and patience.

The sense of hearing is very important for any living being. It is the ever-alert sense of warning and the underlying force of human communication. Loss of hearing is a very dramatic event. It may lead to suicide. Deaf people are threatened by loneliness and character change. Nevertheless, there is not such a thing as a specific "character" of the deaf. Like everyone else, deaf people, old or young, may be quiet or temperamental, stupid or intelligent, or gentle or aggressive. The one thing they have in common is discouragement about conquering the hearing world. The great problem of children who are born deaf is their inability to acquire language. The differences in language acquisition between children who do and do not hear are amply discussed, as well as the enormous problems of parents who have to deal with the upbringing of deaf children.

REFERENCES

1. Frey H. Psychological aspects of deafness. J Laryngol Otol 1941; 56:81-100.

2. Ewing AWG. The nature of deaf mutism — childhood and adolesence. J Laryngol Otol 1943; 58:143-50.

3. Veeneklaas GMH. Meedelen van en meedelen in diagnoses. Nederl Tijdsch Geneesk 1960; 104:1405-9.

4. Buck P. The child who never grew. London: Methuen, 1951.

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INTERSPECIALTY FACIAL SURGERY CONGRESS FOR AESTHETIC, CANCER AND RECONSTRUCTIVE SURGERY

The IFSCACRS will be held at the Waldorf-Astoria in New York, April 27-30, 1983. This Congress is sponsored by the International Oculoplastic Society. For more information contact Pierre Guibor, MD, IFSC Secretary, 630 Park Avenue, New York, NY 10021; (212) 734-1010.

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FOURTH WORLD CONGRESS ON BRONCHOESOPHAGOLOGY

The Fourth World Congress on Bronchoesophagology will take place at the Foresta Conference Center in Stockholm, Sweden, June 20-23, 1983. This Congress is arranged by the International Bronchoesophagological Society, Swedish Otolaryngological Society and Swedish Society for Pulmonary Diseases. During the meeting, the Congress will update the knowledge within bronchology and esophagology. Further information may be obtained by writing IBES Congress 1983, c/o RESO Congress Service S-105, 24 Stockholm, Sweden, or Dr. Stig Haglund, Secretary of the Congress, Dept. of Otolaryngology, Karolinska Sjukuset, S-104 01 Stockholm 60, Sweden.

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WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XIIIth World Congress of Otorhinolaryngology will be held in Miami Beach May 26 — June 1, 1985. For further information please contact Anthony J. Maniglia, MD, Secretary-General, P.O. Box 016960 (D-48), Miami, FL 33101.

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SUPRAGLOTTIC LARYNGECTOMY: 30 YEARS OF EXPERIENCE

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A review of 467 cases of supraglottic laryngectomy operated during the last 30 years is presented. Cases have been subdivided into groups according to stage and TNM classification. By far the most numerous in this series were T2 cases. N0 cases prevailed over N+ by 4:1. Stage II cases represented about 60% of the total. Results are analyzed according to TNM and staging. The average overall 5-year cure rate is 75%. The influence of factors other than TNM and staging upon results is also considered. Supraglottic laryngectomy may be extended to include one arytenoid, the base of the tongue, or both, with approximately equal results. Practically all cases had en bloc bilateral functional or classic neck dissection for threatening or actual lymph node metastases. This may have contributed to a higher number of successes. Combined surgery and radiotherapy is occasionally indicated, but rarely improves the prognosis of severe cases. Site and type of recurrences are considered and their treatment and prognosis are discussed. On the basis of the present study the clinical value of supraglottic laryngectomy is further assessed.

INTRODUCTION

Since our initial report on supraglottic larygectomy published in this journal in 1968,[1] we have kept substantially to the same principles, and readers may refer to our previous reports for basic technique, indications, postoperative course and complications. The present communication is a statistical analysis of data, namely, classification of cases, number of cures and failures as a function of time, TNM definition, staging, type of surgery, association with radiotherapy, histological type of the tumor and its relationship to the host tissue. We are hopeful that this work, the result of 30 years of experience,[2-10] will provide a useful point of reference for future work.

CASE MATERIAL

Selection of Cases. Since 1951, 467 supraglottic laryngectomies have been performed in our clinic (Fig. 1). Of these cases, 430 were males and 37 females, and the average age was 51 years. For several reasons, only 407 of these cases could be exactly classified and had a regular follow-up. Sixty cases were lost to follow-up after a varying number of months or years, and were not included

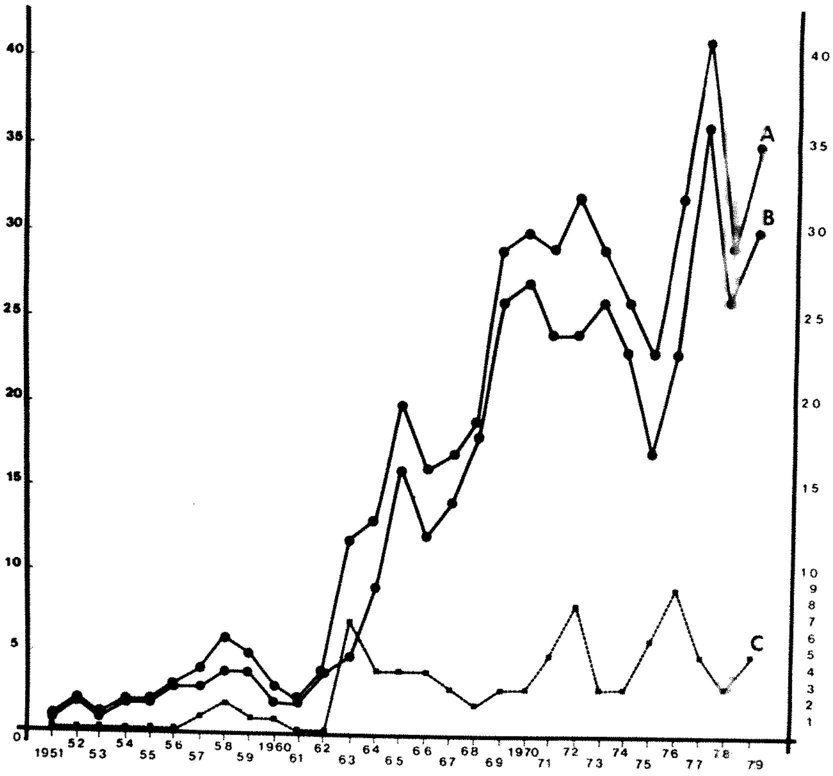

Fig. 1. Supraglottic laryngectomy: number of cases operated per year from 1951 through 1979 and results of surgery. A - Total cases submitted to surgery; B - Free from disease; C - Died of cancer.

From the E. N. T. Clinic, University of Milan.

REPRINTS — Prof. Ettore Bocca, MD, Director, Clinica Otorinolaringologica della Università, Ospedale Maggiore di Milano, Via F. Sforza 35, Milan 20122 Italy.

TABLE 1. TNM CLASSIFICATION*

	N_0	N_1	N_2	N_3	Total
T_1	44	12	2	1	59
T_2	203	74	16	3	296
T_3	—	—	—	—	—
T_4	30	17	3	2	52
Total	277	103	21	6	407

*All cases M_0 on first examination.

TABLE 2. STAGING

Stage I	51 (12.53%)	T_1N_0	44
		T_1N_{1a}	5
		T_1N_{2a}	2
Stage II	235 (57.73%)	T_2N_0	203
		T_2N_{1a}	29
		T_2N_{2a}	3
Stage III	115 (28.25%)	T_1N_{1b}	7
		T_2N_{1b}	45
		T_2N_{2b}	13
		T_4N_0	30
		T_4N_{1a}	7
		T_4N_{1b}	10
		T_4N_{2a}	0
		T_4N_{2b}	3
Stage IV	6 (1.47%)	T_1N_3	1
		T_2N_3	3
		T_4N_3	2
Total	407		407

TABLE 3. CORRECT OR INCORRECT DIAGNOSIS OF N AS DETERMINED BY HISTOPATHOLOGIC EXAMINATION

	No.	Correct Diagnosis	False Positive Diagnosis	False Negative Diagnosis
N_0	277	244 (88%)	0	33 (12%)
N_{1a}	41	37 (90.25%)	0	4 (9.75%)
N_{1b}	62	40 (64.52%)	22 (35.48%)	—
N_{2a}	5	2 (40%)	0	3 (60%)
N_{2b}	16	11 (68.75%)	5 (31.25%)	—
N_3	6	6 (100%)	0	—
Total	407	340 (83.54%)	27 (6.63%)	40 (9.83%)

in the present survey. There has been a 5-year follow-up for 377 cases.

TNM Classification and Staging. Table 1 shows TNM distribution. Although the classification of T for the supraglottic region is unsatisfactory, both in the 1969 and 1974 Union Internationale Contre le Cancer (UICC) publications, we prefer the 1969 classification because of better definition of T_1 and T_2.

The absence of T_3 in our classification is not accidental, but is due to the fact that T_3, as defined in the UICC publications of 1969 and 1974, is most often *not*, or *no longer*, a supraglottic tumor, and therefore it is not amenable to supraglottic surgery. Moreover, in the present classification, invasion of the arytenoids and/or aryepiglottic and pharyngoepiglottic folds, and/or vallecula and base of the tongue, and/or preepiglottic space are all indicated as T_4, in the absence of any better indication offered either in 1969 or in 1974 UICC publications.

In Table 2, which shows the TNM distribution and staging, the N− (N_0, N_{1a}, N_{2a}) group is much greater than the N+ group (N_{1b}, N_{2b}, N_3) 323 against 84). We have strictly observed the TNM recommendation in the classification of N, although we feel that the subdivision into *a* and *b*, designating nodes considered to contain or not to contain growth respectively, is confusing. M+ cases have never been observed on first examination, although late distant metastases have been observed in eight of our N_2 and N_3 cases.

Inasmuch as practically all cases were subjected to bilateral elective or curative neck dissection (functional[11] or classic), Table 3 shows figures and percentages of correct or incorrect guesses concerning metastases of lymph nodes in relation to classification of N0. It is noteworthy that 13.16% of all N_0, N_{1a} cases showed histological evidence of cancer dissemination. This further justifies our assumption that elective neck dissection should be performed in all supraglottic cancers, even when no clinical evidence of lymph node metastases is present.

RESULTS

Surgery. Of all cases operated 75% are alive and well five years after the operation. Figure 2 reveals that the survival rate has a tendency to diminish as a function of time and of higher staging. Figure 3 shows the incidence of recurrences as a function of time and Table 4 shows the incidence of recurrences, their distribution from stage I to stage IV and their location. Distant metastases occurred in eight cases, and were the ultimate cause of death.

Combined Radiosurgical Treatment. Forty-eight cases (20% of 241 supraglottic laryngectomies

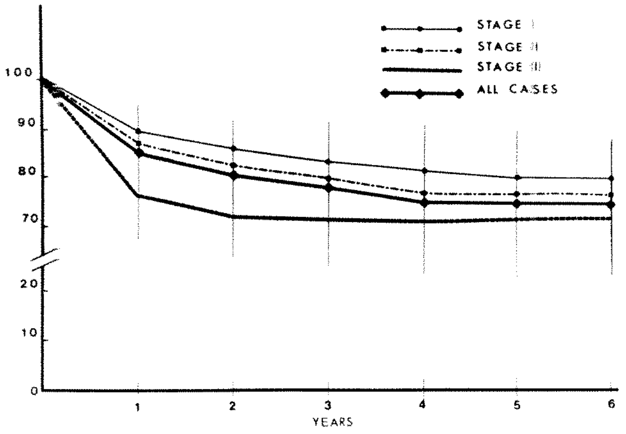

Fig. 2. Percent average survival as a function of time according to stage. Stage IV is not represented because of the exceedingly small number of cases.

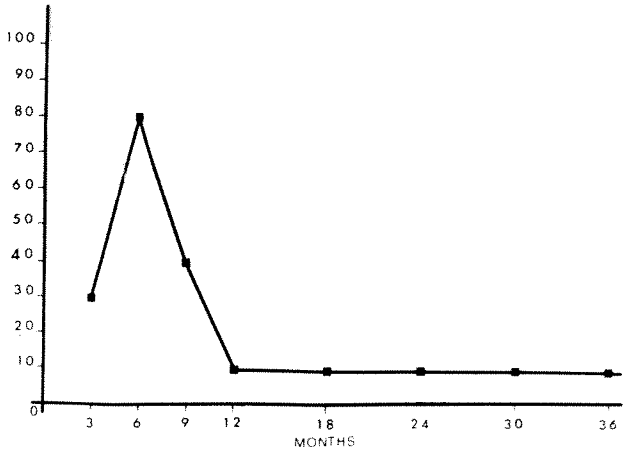

Fig. 3. Percent distribution of recurrences as a function of time after operation.

TABLE 4. RECURRENCES ACCORDING TO STAGE, TN, AND SITE DISTRIBUTION

Stage	*No. Cases*	*Recurrences* *Local: Laryngopharynx or Tongue*	*Neck*	*Total Recurrences*	*Distribution of Recurrences According to TN Classification* *Local: Laryngopharynx or Tongue*		*Neck*	
Stage I	43	4 (9.30%)	1 (2.32%)	5 (11.62%)	T_1N_0	1	T_1N_{2a}	1
					T_1N_{1a}	3		
Stage II	222	33 (14.86%)	3 (1.35%)	36 (16.21%)	T_2N_0	20	T_2N_0	3
					T_2N_{1a}	13		
Stage III	106	16 (15.09%)	13 (12.26%)	29 (27.35%)	T_1N_{1b}	1	T_1N_{1b}	2
					T_2N_{1b}	3	T_2N_{1b}	6
					T_4N_0	7	T_1N_{2b}	4
					T_4N_{1a}	3	T_2N_{2a}	1
					T_4N_{1b}	1		
					T_4N_{2b}	1		
Stage IV	6	2 (33.33%)	0	2 (33.33%)	T_2N_3	2		
Total	377	55 (14.59%)	17 (4.50%)	72 (19.09%)		55		

operated between 1965 and 1974) received radiotherapy combined with surgery (Tables 5 and 6). Thirteen cases had preoperative irradiation, limited to 5000 rads, while 35 had postoperative irradiation at doses varying from 6000 to 6500 rads or more.

Preoperative irradiation was given to the larynx if there was wide extension of the tumor; postoperative irradiation was given to the neck in cases with advanced lymph node metastasis with capsular rupture, as demonstrated by histological examination. All but three cases belonged to stage III.

Failures occurred in only 2 of the preoperative group (15%) while there were 17 (48%) in the postoperative group. This further confirms that the fate of supraglottic cancer is governed much more by the degree of invasion of the lymph nodes than by the type and extension of the primary.

It is our impression, after comparing two successive periods of ten years, in the second of which combined therapy was never applied, that the prognosis for advanced cases is not distinctly improved by the association of radiotherapy with surgery.

TABLE 5. RESULTS AMONG ALL PATIENTS RECEIVING RADIOTHERAPY AND SUPRAGLOTTIC LARYNGECTOMY (1965-1974)

Total No. SG	*No. Cases Submitted to Radiation* *Preop*	*Postop*	*Recurrence*	*Results* *Alive and Well*	*Died from Nontumor Disease*
		SSG = 26			
241	48 (19.91%)		17 (35.41%)	29 (60.43%)	2 (4.16%)
		ESG = 22			

SG - Supraglottic laryngectomy; SSG - Standard supraglottic laryngectomy; ESG - Extended supraglottic laryngectomy.

TABLE 6. COMBINED SURGERY AND RADIOTHERAPY IN STANDARD AND EXTENDED SUPRAGLOTTIC LARYNGECTOMY (1965-1974)

Type of Operation	*TNM**	*No.*	*Preop*	*Postop*	*Radiotherapy Results* *Alive and Well*	*Died from Cancer*
SSG (N = 26)	T_1N_{1b}	4	—	4	2	2
	T_1N_{2b}	1	—	1	1	—
	T_2N_0	4	2	2	2	—
	T_2N_{1a}	1	1	—	1	—
	T_2N_{1b}	11	—	11	6	5
	T_2N_{2b}	2	—	2	—	2
	T_4N_0	1	—	1	—	1
	T_4N_{1b}	2	—	2	2	—
ESG (N = 22)	T_2N_0	4	3	1	3	—
	T_2N_{1b}	5†	2	3	2	2
	T_2N_{2b}	2†	—	2	—	1
	T_4N_0	5	2	3	3	2
	T_4N_{1a}	3	2	2	2	1
	T_4N_{1b}	3†	2	1	2	—
Total		48	13	35	26	16

SSG - Standard supraglottic laryngectomy; ESG - Extended supraglottic laryngectomy.

*All cases M0 on first examination.

†One patient lost to follow-up.

TABLE 7. NUMBER OF DEATHS AMONG EXTENDED SUPRAGLOTTIC LARYNGECTOMY CASES (N = 59)

Type	*No. Cases*	*Death from Cancer*
1	31	3
2	17	5
3	11	4
	Number of failures	12 (20.33%)
	Local recurrences	9 (15%)
	Neck recurrences	5 (8%)

Such cases generally respond equally well, or equally badly, with radiotherapy alone or with surgery alone.

However, we advise postoperative radiation to the neck in all N+ cases where histological examination shows capsular rupture. At the same time, we do not advise preoperative radiation to the larynx, with a few exceptions for which no rule may be set. Supraglottic surgery should never be considered if site and spread of the growth exceeds the limits for its indication from the beginning. Retrieving such limits by radiotherapy proves most often to be a dangerous illusion.

Expansion of Indications for Supraglottic Laryngectomy. After 1970, in a growing number of cases indications for supraglottic laryngectomy have been extended to include cases where the tumor-spread involved the epilarynx, the medial wall of the upper piriform fossa, one of the arytenoids, the vallecula or the base of the tongue.[12,13] Such extended supraglottic laryngectomy may be divided into three different types:

1. Lateral and posterior extension (aryepiglottic fold, arytenoid, and medial wall of pyriform fossa).
2. Anterior extension (base of the tongue).
3. Combined anterior and posterolateral extension (base of the tongue plus one arytenoid and adjacent medial wall of pyriform fossa).

Extended supraglottic laryngectomy was carried out in 67 cases (14.35% of the total number). These were divided as follows: type 1 — 36, type 2 — 25, type 3 — 11. Whenever the arytenoid must be included in the surgical specimen, its vocal process is preserved and fixed to the cricoid cartilage in the midline with monofilament 3/0 steel wire. This measure prevents untoward sequelae concerning phonation and deglutition. The results of this approach, limited to 59 cases with at least three years follow-up, are shown in Table 7.

The extended supraglottic technique may improve the prognosis of many cases where local spread makes radical surgery doubtful with the standard technique, and therefore should be effected more often than it usually is today.

TABLE 9. HISTOLOGICAL GRADING (N = 30)

Group	*Grade 1**	*Grade 2†*	*Grade 3§*
A (recurrence)	1	8	6
B (no recurrence)	8	6	1

*Highly differentiated.
†Moderate.
§Poor.

TABLE 10. MODALITY OF LOCAL SPREAD (N = 30)

Group	*Sharp Borders*	*Ill-defined Borders*	*Plurifocal*
A (recurrence)	3	10	2
B (no recurrence)	12	3	0

TABLE 11. PERITUMORAL PAPILLOMATOSIS OR CA IN SITU (N = 30)

Group	*Papillomatosis*		*Ca in situ*
	Absent	*Present*	
A (recurrence)	3	10	2
B (no recurrence)	12	3	0

TABLE 12. STROMAL REACTION (N = 30)

Group	*Absent*	*Present*	
		True	*False*
A (recurrence)	9	5	1
B (no recurrence)	3	9	3

TABLE 13. LYMPHOCYTE AND PLASMACELLULAR LOCAL RESPONSE (N = 30)

Group	*Absent*	*Poor*	*Moderate*	*Strong*
A (recurrence)	5	5	3	2
B (no recurrence)	0	2	4	9

Factors Influencing Results Other Than TNM and Stage. The influence of several histopathological factors upon the cure rate of supraglottic laryngectomy was the subject of a detailed investigation; equal numbers of surgical specimens pertaining to cases belonging to the same TNM and stage groups, but showing different long-term results, were serially sectioned.[14] Tables 8 to 13 show the influence of these factors upon the incidence of recurrences.

Local Recurrence: Treatment and Prognosis. In Tables 14-16, 35 out of 55 local recurrences were carefully analyzed. At least six patients who presented with intrinsic recurrences and died from cancer could probably have been saved by primary total laryngectomy. All the rest could not have been saved from recurrence even by total laryngectomy. Although an indiscriminately conservative attitude should be discouraged, the number of failures observed is certainly not high enough to invalidate the principles of supraglottic laryngectomy. However,

TABLE 8. MACROSCOPIC ASPECT OF TUMOR (N = 30)

Group	*Vegetating*	*Infiltrated*	*Vegetating & Ulcerated*	*Vegetating & Infiltrated*	*Ulcerated & Infiltrated*
A (recurrence)	1	1	4	2	7
B (no recurrence)	11	1	1	2	0

TABLE 14. RECURRENCES AFTER SUPRAGLOTTIC LARYNGECTOMY (N = 377)

Site	*No.*
Laryngopharynx or tongue	55 (14.58%)
Neck	17 (4.51%)
Total	72 (19.09%)

TABLE 15. CURE RATE OF RECURRENCES ACCORDING TO SITE

Recurrences	*3 Years*	*5 Years*
Intrinsic	10:15 (66.6%)	8.15 (53.33%)
Extrinsic	5.20 (25%)	1:20 (5.0%)
Total	15:35 (42.85%)	9:35 (25.71%)

TABLE 16. CURE RATE OF RECURRENCES ACCORDING TO TREATMENT

Treatment	*3 Years*	*5 Years*
Secondary surgery	7:16 (43.75%)	5:16 (31.25%)
Radiation	8:19 (42.0%)	3:19 (15.78%)

it is hoped that even this limited number of recurrences could be further reduced through more accurate indications and more careful technique.

Neck Recurrence: Treatment and Prognosis. Although no exact figure is available, our feeling is that about 80% of neck recurrences are not due to faulty technique in neck dissection, but to capsular rupture and dissemination outside the lymph nodes. Nearly all neck recurrences (96%) were observed in N2, N3 cases and only a few proved to be "forlorn" lymph node invaded by cancer.[15]

As a rule, neck recurrences are represented by solid, noncapsulated cancerous masses colonizing the soft tissues of the neck. As such, they are beyond reasonable hope of cure, whichever form of treatment, single, or combined, we choose to adopt: surgery, radiation, chemotherapy, immunotherapy.

CONCLUSIONS

The clinical value of supraglottic laryngectomy in the management of supraglottic cancer is further confirmed by the present study. A 5-year cure rate of about 75% of all cases may be expected, ranging from about 90% in stage I to about 65% in stage IV. As a matter of fact, these figures, controlled over a long period of time on a great number of cases, are not subject to significant variations and tend to repeat themselves year after year. A reasonably accurate prediction of results is therefore possible. Considering that most recurrences appear within 12 months after the operation, permanent cure may be considered as highly probable at the end of the first postoperative year. In effect, comparative elaboration of data concerning all cases operated up to one year ago, and a more limited group with regular check-ups for at least four years postoperatively, shows only minor changes in percentage of cures. Probably our most favorable figures also depend on the fact that elective bilateral functional neck dissection was routinely performed in nearly all cases.

If one considers that the percentage of permanent cures for the N+ group drops by about 15% as compared with the N0 group, and that about 13% of N0 cases showed histological lymph node dissemination, the influence on long-term results of systematic regional surgery for supraglottic cancer must be emphasized. The ill fate of late recurrences in untreated necks is well known.

X-ray therapy should be given in association with surgery in cases where local or regional spread makes radical surgery doubtful and prognosis poor. However, it is our impression that prognosis is generally not improved by such association. Preoperative routine irradiation is not followed by any demonstrable improvement of results.

As a final statement we can say that when diagnosis is correct, indications are precise, and technique is appropriate, supraglottic laryngectomy combined with elective or curative bilateral neck dissection is still, at this time, the best weapon in our hands for the control of supraglottic cancer.

REFERENCES

1. Bocca E, Pignataro O, Mosciaro O. Supraglottic surgery of the larynx. Ann Otol Rhinol Laryngol 1968; 77:1004-26.
2. Bocca E. Il cancro del vestibolo laringeo. Arch Ital Otol 1953 Suppl 14:65-102.
3. Bocca E, Cova PL, Pignataro O. Il cancro dell'epiglottide. Tumori 1961; 47:107-30.
4. Bocca E. Supraglottic laryngectomy and functional neck dissection. J Laryngol Otol 1966; 80:831-8.
5. Bocca E, Pignataro O. Considérations sur l'état actuel de la chirurgie conservatrice et reconstructive du cancer du larynx. Ses résultat. Rev Laryngol Otol Rhinol 1972; 93:79-87.
6. Bocca E. Possibilità di chirurgia funzionale nel cancro laringeo. Tumori 1974; 60:475-8.
7. Bocca E. Il ricupero degli insuccessi degli interventi funzionali. Tumori 1974; 60:553-5.
8. Bocca E. Supraglottic cancer. Laryngoscope 1975; 85: 1318-26.
9. Bocca E. Rapporti tra chirurgia e radioterapia nei carcinomi della laringe. Minerva Med 1980; 71:335-9.
10. Bocca E. Supraglottic laryngectomie. Twintigste Jaarboek Van Kankerbristrijng in Nederland 1970; 125-8.
11. Bocca E, Pignataro O. A conservation technique in radical neck dissection. Ann Otol Rhinol Laryngol 1967; 76:957-87.
12. Bocca E. La laryngectomie sus-glottique élargie. Indications et possibilités. Nuovo Arch Ital Otol 1974; 2:252-6.
13. Pignataro O, Bocca E. Laryngectomie sus-glottique élargie dans les cancers de l'épiglotte envahissant la vallécule et la base de la langue Acta Otorhinolaryngol Belg 1980; 34:646-51.
14. Leonardelli GB. Cause di recidivanza locale del cancro vestibolare. Nuovo Arch Ital Otol 1976; 4:353-67.
15. Pignataro O, Bocca E. Indications et limites de l'évidement fonctionnel du cou dans la chirurgie du cancer du larynx: résultats de 18 ans. Compt Rend 77 Congr Soc Franc ORL, Arnettet Ed (Paris). 1980; 574-6.

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ESTIMATING EIGHTH NERVE SURVIVAL BY ELECTRICAL STIMULATION

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Determining nerve survival is important in selecting patients for cochlear implants, and in predicting outcomes from such implants. In search of a possible method we deliberately destroyed nerve fibers (ganglion cells) in 17 cat cochleas to produce a range of degenerations. Months later, we electrically stimulated these ears (and seven controls) and recorded electrical ABR input-output functions. Cats with no surviving ganglion cells showed no ABR activity. Cats with 5%-10% surviving cells had ABRs which typically had normal thresholds but decreased input-output functions. The suprathreshold slopes of these input-output functions reliably predicted ganglion cell survival for all degrees of degeneration. Thus, perceptual (or electrical) threshold is a poor indicator of nerve survival. Loudness growth (or growth in the electrically-induced auditory brainstem response) is a good index of surviving ganglion cells.

One of the variables affecting the theoretical success of an individual's cochlear implant (single- or multichannel) is the number of surviving spiral ganglion nerve fibers. Our study examines the possibility of using electrically-induced auditory brainstem response (EABR) for predicting surviving spiral ganglion nerve fiber populations.

We first damaged 17 cats ears (nine cats) with aminoglycosides, surgical trauma, or freezing, to produce graded degrees of nerve degeneration. Three to six months later we electrically stimulated these ears and those of seven controls, with standardized electrical pulses just inside the round window (RW) (scala tympani [ST]) and recorded the EABR. We then compared the EABR thresholds and amplitude growth curves with microscopic estimates of surviving spiral ganglion cells.

Several investigators have attempted to estimate the viability of auditory nerve fibers by electrical stimulation in both deaf humans and in animals, some of whom were deafened. House and Brackman used an electrode on the promontory of the cochlea to obtain a perceptual threshold response as a means of selecting cochlear implant candidates. These results have been unreliable in practice.[1] Merzenich and White recorded EABRs in normal cats and studied effects of ST spacing of bipolar electrodes.[2] They concluded that the amplitude and slope was a monotonic function of the number of nerve fibers excited. Walsh and Leake-Jones used serial EABRs as one method of estimating damage due to chronic electrode placement in the ST, intense electrical stimulation and the progressive effects of acute neomycin infusions.[3] They observed that the growth of the EABR was sensitive to modifications in the population of excitable neural elements. Some histological verification was done, but the relationships were, in their words, "not quantitatively studied." Several others have electrically stimulated the cochlea and recorded EABRs, or responses collected from several auditory CNS structures. Their observations, however, do not bear directly on the nerve viability problem and will not be reviewed here.

Two studies provide technically important background information on electrical artifact problems and on differences caused by site of stimulation.

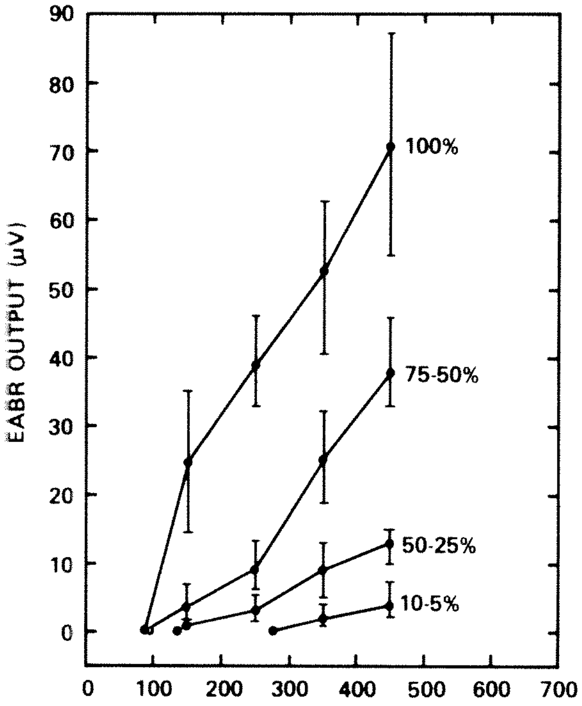

Fig. 1. Input-output EABR functions for cats with normal (100%) and varying degrees of spiral ganglion cell losses (75-50%, 50-25%, 10-5%). Vertical bars show total range. Points of measurements are illustrated in Figs. 2-4.

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EABR AND HISTOLOGIC FINDINGS FOR CAT COCHLEAS (N = 24)

Cat No.	Mode of Damage	% of Ganglion Cell Survival					EABR Threshold µA	EABR Maximum Amplitude µV
		LB	UB	LM	UM	A		
32 R&L, 69L 50 R, 70 R&L	4	100	100	100	100	100	60-100*	50-83
50 L†	4	100	100	100	100	100	100	35
60 L	3	75	75	100	100	100	100	76
60 R	3	75	75	100	100	100	100	68
52 L	3	50-75	50	50	75	75	100	50
52 R	3	25-50	50	75	75	100	90	37
56 L	1 & 3	5	5	5-10	5	5	170	7
56 R	1 & 3	0	0	10	0	5-10	270	7
69 R	2	0	25	25	50	100	230	22
12 L	1 & 2	25-50	25	50	75	100	100	28
12 R	1 & 2	25-50	50	50	100	100	60	40
37 L	1	0-25	25-50	25-50	25-50	50	100	15
37 L	1	25	25-50	25-50	50	100	100	12
48 L	1 & 2	0	0	0	5	5	425	3
48 R	1 & 2	0	0	0	5	5	300	7
3 R&L - 4 R&L	1 & 2	0	0	0	0	0	NR	NR

LB - Lower basal turn, UB - Upper basal, LM - Lower middle, UM - Upper middle, A - Apical.
1 - Perfused or systemic aminoglycosides, 2 - Surgical trauma, 3 - Freezing, 4 - No damage.
*Mean threshold - 90 µA.
†Normal cochlea but chronic otitis media and granulation tissue in the round window.

Yamane et al, using guinea pigs, were able to confirm Simmons and Glattke's earlier suspicion that low-intensity stimulations of the RW membrane can create an "electrophonic" EABR response which is not present in neomycin-treated controls.[4,5] They once again pointed out that the EABR is subject to contamination by muscle twitching. In a companion paper, Marsh et al,[6] explored the guinea pig's EABR according to the site of stimulation. Round window, ST or scala vestibuli (SV) stimulations had about the same thresholds (200-800 µA) and input-output functions, while modiolar stimulation thresholds were between about 50 and 500 µA.[6] Dobie and Kimm recorded EABRs before and after sectioning the vestibular nerve and the auditory nerve in monkeys.[7] They demonstrated that auditory nerve was the only contributor to the EABR.

METHODS

Seventeen cat ears (nine cats) were damaged with either (or a combination of) pharmacologic, mechanical, or physical trauma. Kanamycin 400 mg/kg intraperioneal and 400 mg intracochlear perfusion (via RW puncture) and stapes avulsion were administered. A liquid nitrogen probe was placed on the promonotory for 10-15 minutes in other animals. Mechanical trauma was induced by probing a straight pick into the modiolus via the RW.

Three to six months later an EABR was performed under Nembutal anesthesia on each of the damaged cat ears and the seven controls. An 0.1-mm ball-tipped stainless steel electrode was inserted about 1 mm into the ST of both ears. A stainless steel screw in the frontal sinus bone was used as the vertex electrode and a ground electrode was inserted into the neck muscles. The electrical stimulus was a monopolar 0.5-ms biphasic charge-balanced pulse at 10/s. The EABR was recorded differentially between the opposite ST electrode and frontal sinus electrode. A preamplifier with band-pass filters of 0.2 Hz to 10 kHz amplified the signal 100 times. The signal was then processed by a digital computer for 256 samples. The EABR responses were displayed on an oscilloscope, stored on tape, and X-Y plotted off-line from the tape.

Threshold was determined as the first detectable and repeatable baseline deflection outside the stimulus artifact zone, typically at 2.6-2.8 ms. The suprathreshold peak-to-peak amplitude of this same wave was used to measure the input-output functions. The stimulus current was increased in 50- or 100-µA increments after threshold was established. EABR recordings were made at all of these levels. The increments in stimulus were terminated when facial muscle twitching was seen or when this twitching interfered with accurate EABR measurements.

The animals were sacrificed and the temporal bones were removed. Immediate oval and RW infiltrations with iced phenol were performed. Decalcification, embedding, hematoxylin-eosin staining, and sectioning were then performed. Serial sections were mounted at 100 µ intervals. The spiral ganglion neuron populations in the lower basal, upper basal, lower middle, upper middle and apex turns were estimated as quartiles between normal and no ganglion cells by two observers. This data was stored and later correlated with the EABR amplitude growth curve and threshold response level for each animal.

RESULTS

EABR threshold was a poor predictor of surviving neurons. The slope and magnitude of the input-output functions proved to be reasonably accurate. Figure 1 shows these thresholds and functions for all cats, sorted into quartiles of residual ganglion cells. The degree of damage to ganglion cells was sufficiently varied among ears to permit good correlations in an admittedly limited sample. The Table lists the pertinent measurements for the total population of experimental animals. Note that only total degeneration resulted in total elimination of the EABR.

An elevation in EABR threshold only occurred in ears with 5% or less residual ganglion cells in the lower basal turn. We have the impression, but an inadequate number of observations to conclude, that probably as few as 10% residual cells could have produced a threshold within the normal

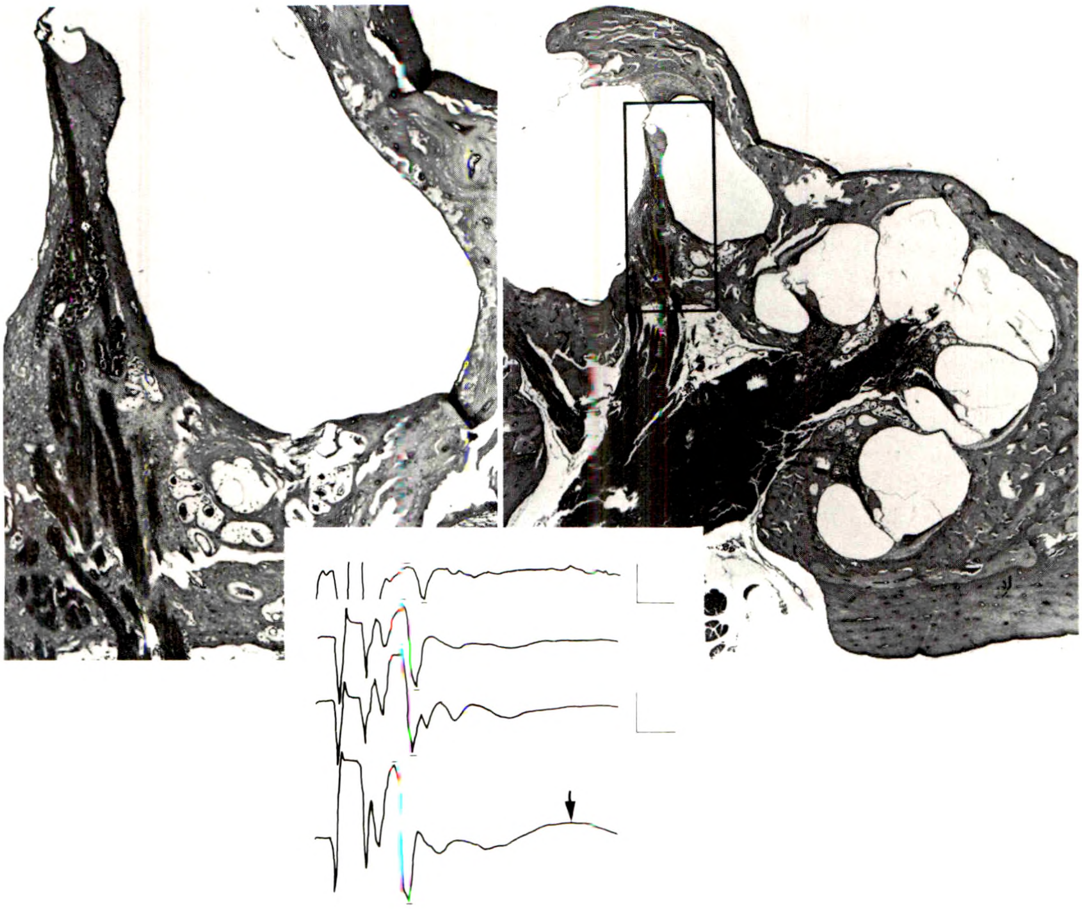

Fig. 2. Photomicrographs and illustrative EABR waveforms for normal population of cat cochlea ganglion cells. Right, midmoliolar section. Left, enlargment of lower basal cochlear segment outlined on right. Typical EABR waveforms from slightly above threshold to near maximum, redrawn from original tracings, have marks indicating measurement points. Beginning of seventh nerve response (arrow) is seen in lower-most waveform. (Scale: 1 ms and 3 μV - Upper traces; 1 ms and 28 μV - Lower traces.)

range. Normal for our stimulus was 90 μA, ± 30 μA.

The suprathreshold EABRs were very good predictors of surviving ganglion cells. Note that in the Figure 1 data there was no overlap in the input-output functions, once near-threshold measurements were exceeded. These functions predicted nerve survival for 75% of the cochlea, but did not predict survival in the most apical segment quite as accurately. The slope of our normal EABR is about the same as Merzenich and White's data for widely spaced bipolar ST electrodes. However, their thresholds were considerably higher than ours (90 v 400 μA).

Figures 2 to 4 are typical EABRs and photomicrographs for three ears: a normal with 100% ganglion cells, an ear with about 50% degeneration (with total lower basal turn loss), and another with near-total ganglion cell loss throughout the cochlea. Index marks on the waveforms show where we chose to make our EABR amplitude measurements for the composite Figure 1 data. The median latency for the initial deflection was 2.7 ms, ± about 0.3 ms.

Stimulation spread to the seventh nerve routinely occurred in the vicinity of 375-550 μA in all experiments where notes on this excitation were kept. The seventh nerve contractions were visible at about the same stimulus intensities which caused a deflection in the EABR. Figure 2 shows one example.

DISCUSSION

Our reason for making these measurements was to forward the development of a method to access ganglion cell survival in vivo in humans. It is a simple, low-risk procedure to temporarily place a comparable electrode in the same ST location and apply these same stimuli. Readout by EABR and by perceptual reports (threshold to maximum loudness, with scaling, for example) can easily be done. It is critically important to do these kinds of studies, even though the implanting surgeon is already committed to stuffing an electrode (or several) into the patient's ear. The truth of the moment is that no one really is able to predict a "successful" result from a failure. Unless we develop better means of decision-making, there are going to continue to be too many unexplained differences in results in an al-

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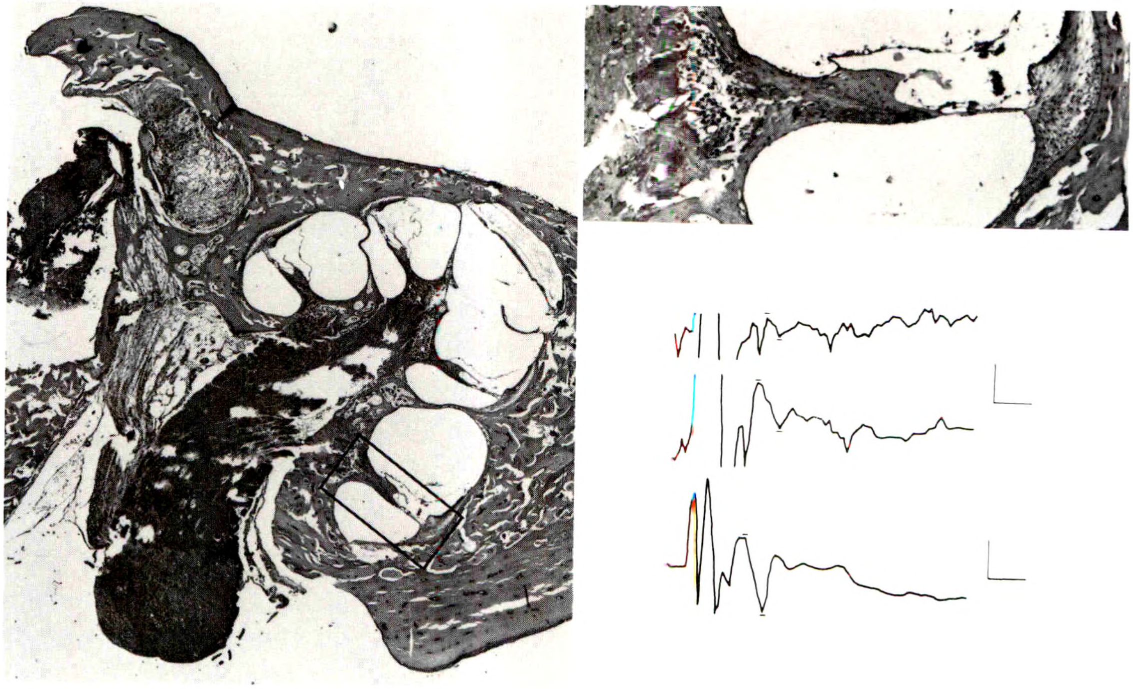

Fig. 3. Photomicrographs and EABRs of cat cochlea judged to have 50% surviving ganglion cells. Some effects of surgical trauma can be seen in RW and lower basal turn regions where no ganglion cells survived. Enlargement (upper right) is from outlined area of upper basal coil. See Fig. 2 for EABR details and scale.

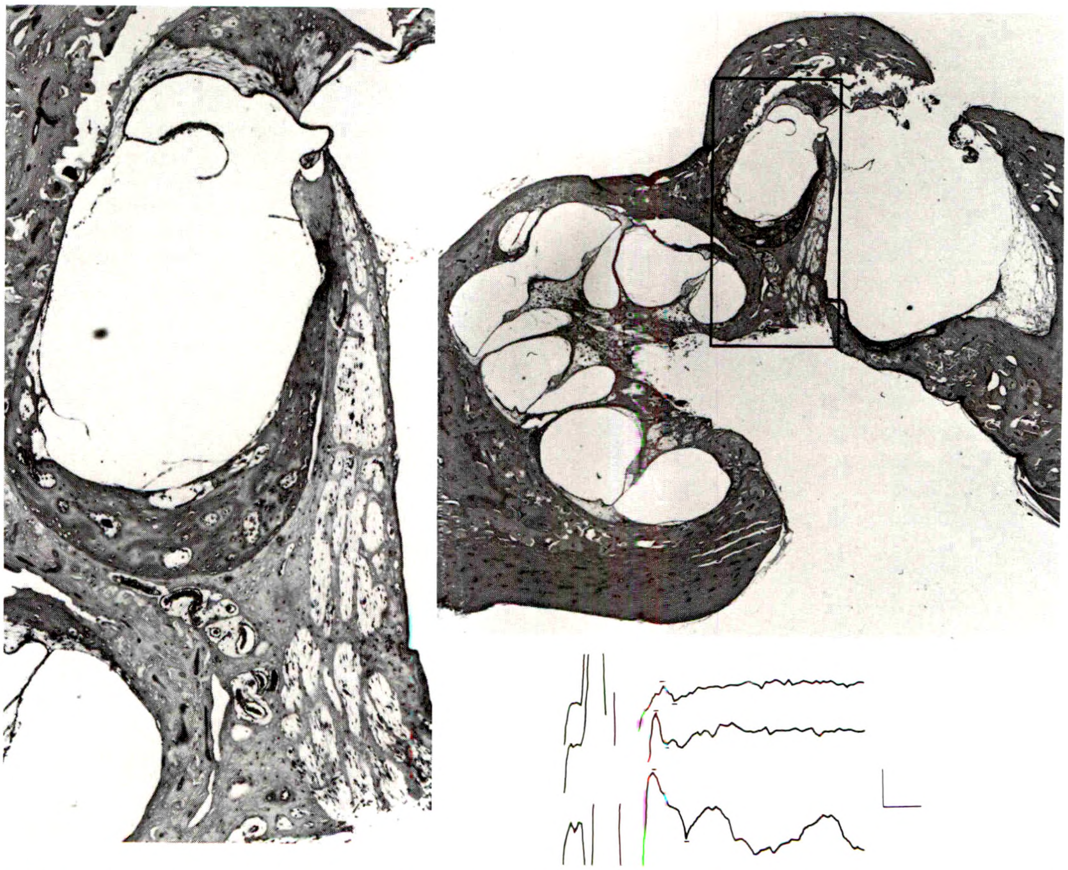

Fig. 4. Photomicrographs and EABRs of cat cochlea with near total loss of ganglion cells. Left, enlargement of lower basal segment outlined in midmodiolar photograph (right). Contents of modiolus were avulsed during processing. See Fig. 2 for EABR details. (Scale, 1 ms and 3 μV.)

ready chaotic field of investigation. We find it highly interesting, for example, that there has not been a single case in which a patient failed to hear by electrical stimulation. Yet we know, by animal experimentation, that nerve impulses do not reach the brain in animals with no remaining ganglion cells and that as few as 5% or less ganglion cells produce an EABR.[8] There is also a single electrode-implanted human temporal bone where hearing occurred with considerably less than 1% of fibers present.[9] Is it logical to expect the same results from such ears as for more heavily populated ones? Is there logic in placing a multichannel system in an ear with one remaining fiber?

The data supplied herein can probably be applied directly to humans if the same electrical stimulus in the same location is used. Threshold may be slightly higher because the human cochlea is moderately larger and contains more insulating bones. The pulse width itself and the relative location are probably more critical parameters. Threshold, for example, varied between 200 and 800 μA in the literature cited earlier, and these differences are not all due to differences in the stimulus dimensions, nor to species differences.

ACKNOWLEDGMENT — Les Atlas and Matthew Herndon were responsible for obtaining the more recent loudness data.

REFERENCES

1. House WF, Brackman OE. Electrical promontory testing in differential diagnosis of sensorineural hearing impairment. Laryngoscope 1974; 84:2163-71.

2. Merzenich MM, White MW. Cochlear implant, the interface problem. In: Hambrecht FT, Resnick JB, eds. New York: Marcel Dekker, Inc, 1977.

3. Walsh SM, Leake-Jones PA. Chronic electrical stimulation of auditory nerve in cat: physiological and histological results. J Hear Res 1982; 7:281-304.

4. Yamane H, March RR, Potsic WP. Brain stem response evoked by electrical stimulation of the round window of the guinea pig. Otolaryngol Head Neck Surg 1981; 89:117-24.

5. Simmons FB. Glattke TJ. Comparison of electrical and acoustical stimulation of the cat ear. Ann Otol Rhinol Laryngol 1972; 81:731-8.

6. Marsh RR, Yamane H, Postic WP. Effect of site of stimulation on the guinea pig's electrically evoked stem response. Otolaryngol Head Neck Surg 1981; 89:125-30.

7. Dobie RA, Kimm J. Brainstem responses to electrical stimulation of the cochlea. Arch Otolaryngol 1980; 106:573-7.

8. Simmons FB. Electrical stimulation of the auditory nerve in cats. Ann Otol Rhinol Laryngol 1979; 88:533-9.

9. Johnsson LG, House WF, Linthicum FH. Bilateral cochlear implants: histological findings in a pair of temporal bones. Laryngoscope 1979; 89:759-62.

10. Simmons FB, Mathews RG, Walker MG, White RL. A functioning multichannel auditory nerve stimulator. Acta Otolaryngol (Stockh) 1979; 87:170-5.

ADDENDUM

We have subsequently examined growth of loudness in our own modiolar-implanted human subject and compared his loudness scaling now with similar data obtained almost four years ago.[10] Though there have been changes in the stimulating equipment (and additional limitations placed on peak currents) which make comparisons slightly uncertain, distinct changes have occurred in two (of four) electrodes. The most heavily used electrode now creates about one half the scaled loudness it did originally at the same stimulus intensities. We estimate about 4,000 hours of stimulation. A second electrode, the least used of the four (about 100 hours) also had a substantial drop in loudness. The two intermedially used electrodes showed no change within the accuracy of the scaling methods. Meanwhile, thresholds on all four electrodes have remained the same over four years. Three years ago we tried and failed to obtain an EABR on this subject.

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EFFECT OF HYPERTHERMIA ON THE LARYNGEAL CLOSURE REFLEX

IMPLICATIONS IN THE SUDDEN INFANT DEATH SYNDROME

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A recent study with dogs has defined an age-related period of transient hyperexcitability in the laryngeal adductor neurons. This observation suggests that age-related neurologic instability of laryngeal mechanisms and abnormal laryngeal closure may be a cause of transient upper airway obstruction, inducing potentially fatal central apnea that could result in the sudden infant death syndrome. Since hyperthermia has been implicated as a cofactor in sudden and unexpected infant death, its effect on laryngeal excitability requires clarification. This investigation has found that both the latency and threshold of the laryngeal adductor reflex decreases during hyperthermia. Thus, hyperthermia effectively enhances this reflex during its age-related period of hyperexcitability, and is capable of triggering upper airway-induced central apnea of sufficient severity to result in death. The effect of temperature on latency is attributed to changes in axonal conduction and synaptic transmission velocities. Temperature-dependent changes in synaptic transmission are hypothesized as the cause of the observed threshold changes.

INTRODUCTION

The sudden infant death syndrome (SIDS) is the single most common cause of death during the first year of life, the typical victim being between two and five months of age. Approximately 8,000 infant deaths from SIDS occur annually in the United States.[1] Despite great effort in both clinical and laboratory investigations, detailed pathogenesis of the disease is still veiled in controversy. One major etiologic hypothesis includes the possibility that transient upper airway obstruction during sleep provokes a prolonged diaphragmatic apnea, resulting in death of infants hereditarily predisposed.[2]

Meanwhile, some evidence suggests that hyperthermia participates in SIDS. Retrospective studies indicate that SIDS infants are especially prone to spontaneous hypothermia and hyperthermia.[3] In this connection, autopsies reveal a high incidence of airway infections presumably associated with febrile episodes.[4] Furthermore, a high rate of small bowel findings characteristic of heatstroke has been described in SIDS victims.[5]

In a previous publication, one of our authors reported a period of transient laryngeal hyperexcitability in pups 50 to 75 days of age.[6] Such a critical period for laryngospasm suggests its relationship to a possible etiology of this syndrome. It is important, therefore, to elucidate the influence of hyperthermia on laryngeal excitability, since clinical observations appear to suggest this link.

MATERIALS AND METHODS

Thirteen adult and 19 beagle pups were used in this study. The canine model was chosen because 1) the central organization of laryngeal reflexes is similar in dogs and human beings,[7] and 2) thermoregulatory development of the dog is also similar to that of the human being.[8] Adult dogs were anesthetized with pentobarbital sodium administered intravenously 30-35 mg/kg of body weight. Pups received intraperitoneal pentobarbital sodium 25-30 mg/kg of body weight. An arterial blood gas catheter and venous catheter for intravenous administration of pentobarbital were placed into the femoral vessels. Animals were kept at a stage 3, plane 1 depth of anesthesia during experimentation. A vertical midline neck incision was used to expose the larynx and trachea, and a cannula was inserted through the fourth tracheal ring for unassisted, spontaneous breathing.

The strap muscles were transected at the level of the thyrohyoid membrane to expose the right thyroid ala, which was removed for exposure of the thyroarytenoideus (TA) muscle. The superior laryngeal nerve (SLN) was then identified and divided 2-3 mm proximal to its bifurcation. The proximal SLN was prepared in a mineral oil bath and was attached to a bipolar platinum wire for stimulation. For the purpose of recording, hooked wire electrodes (platinum irridium) were implanted in the TA muscle, the major adductor of the vocal cords. These operative procedures were carried out under magnification (Zeiss operating microscope).

SLN was stimulated with an S-8 stimulator (Grass) at 0.1-15 V, 0.1 ms pulse duration. EMG of the evoked laryngeal closure reflex was displayed on an oscilloscope 5103N (Tektronics), after passing through a DAM 5A differential preamplifier (WP) and a 5A18N dual trace amplifier (Tektronics). Responses were recorded by a 3960 instrumentation recorder (Hewlett-Packard). Simultaneously, respiratory rate was monitored on a model 7 polygraph (Grass) via a P23BC manometer transducer (Statham) linked to a water-filled needle introduced into the thoracic space. Arterial blood gas was analyzed with a PHM71 acid base analyzer (Radiometer).

We adopted a method of body temperature control, allowing the animals to be warmed with an electric blanket or cooled with an ice water bag. Rectal temperature, measured with a YSI telethermometer, could be varied at will between 34°C and 41°C.

In summary, the right SLN was stimulated electrically, and reflex muscle responses were recorded from the ipsilateral TA muscle. Each stimulus was phase-locked to the expiratory segment of the respiratory cycle so as to avoid respiratory-linked variations in threshold responses.

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TABLE 1. THRESHOLD OF ADDUCTOR REFLEX AT 34°C TO 41°C*

Temp C	*A*	*B*	*C*	*D*
34	2.60±1.00	1.80±0.20	0.46±0.00	0.33±0.01
35	2.30±0.20	1.73±0.04	0.48±0.04	0.27±0.04
36	2.20±0.07	1.43±0.18†	0.44±0.05	0.27±0.02
37	2.10±0.03	1.40±0.44	0.38±0.03	0.27±0.03
38	1.68±0.43	0.92±0.43	0.28±0.02	0.19±0.02
39	1.15±0.15	0.68±0.21	0.27±0.05	0.18±0.03
40	0.95±0.07	0.43±0.11	0.26±0.06	0.14±0.04
41	0.98±0.06	0.40±0.06	0.26±0.02	0.12±0.04

A - 3-week-old; B - 6-week-old; C - 12-week-old; D - Adult beagles.

*Threshold in volts ±SD; $p<0.05$.

†$p>0.05$.

RESULTS

The animals were classified into four groups for comparative investigation of postnatal development: 3-week pups, 6-week pups, 12-week pups, and adult dogs. Rectal temperatures immediately after induction of anesthesia measured 36.8±0.2°C in the 3-week pup, 37.3±0.4°C in the 6-week pup, 38±0.2°C in the 12-week pup, and 38.8±0.2°C in adulthood.

Threshold. With respect to postnatal development, normothermic thresholds were in agreement with our previous reports, in which ipsilateral reflex threshold decreased with age (Table 1). In 3-week pups, thresholds were higher than in other age groups at each body temperature, showing a sigmoid curve with temperature increase. The most rapid change in threshold occurred between 37°C and 39°C (Fig. 1A). Six-week pups showed a sigmoid curve similar to that of 3-week pups. The maximum rate of threshold change with respect to temperature appeared to be somewhat less than that shown by the previous age group between 37°C and 39°C (Fig. 1B). In 12-week pups, thresholds of laryngeal reflexes were in general markedly lower (Fig. 1C). In adult dogs, the thresholds were lower than other age groups tested. In comparing

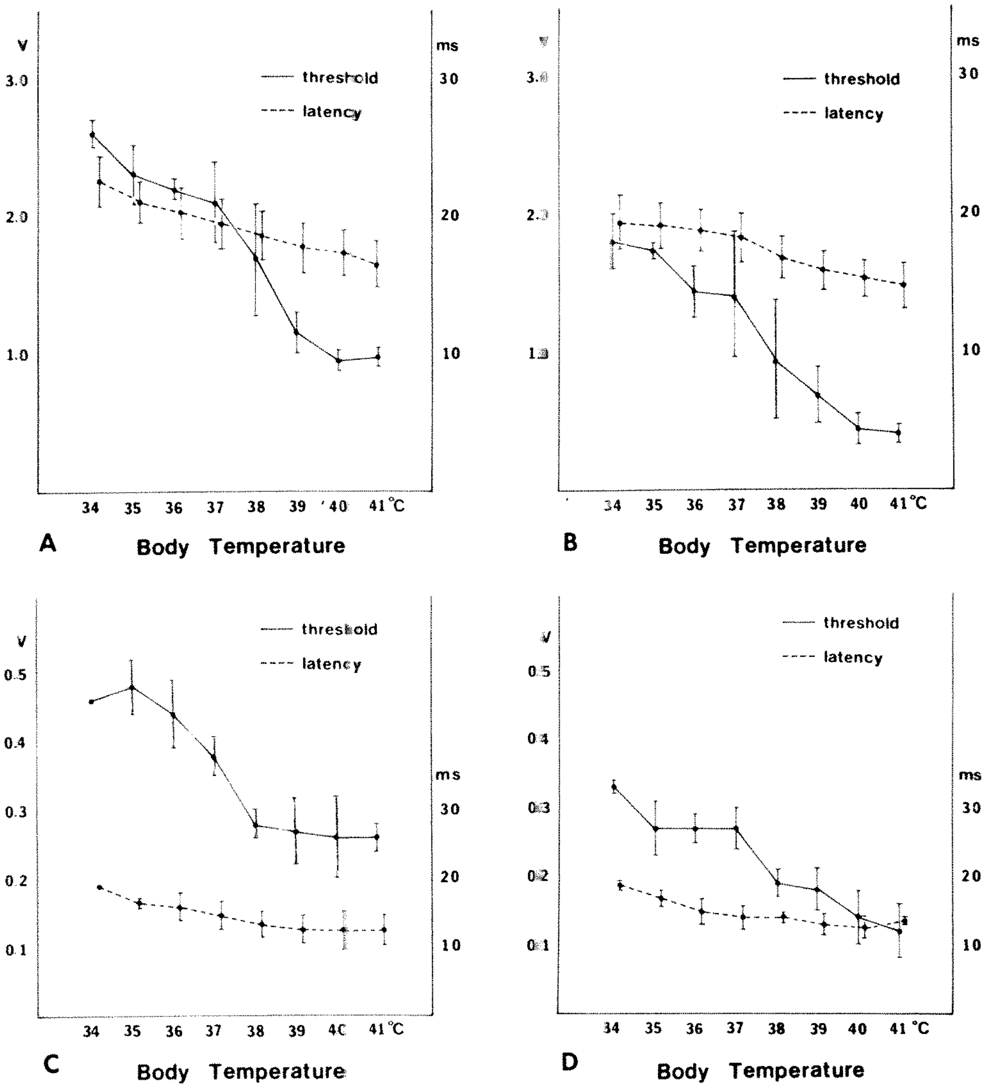

Fig. 1. Influence of body temperature on threshold and latency in A) 3-week-old puppies; B) 6-week-old puppies; C) 12-week-old puppies; D) Adult dogs.

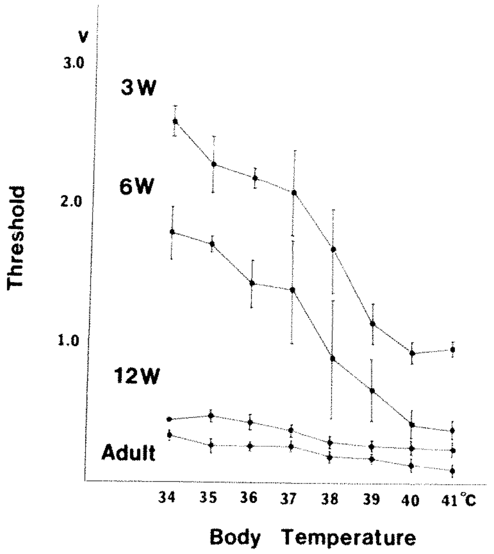

Fig. 2. Influence of body temperature on threshold in four age groups. Note the sigmoid relationship in younger age groups.

threshold change to temperature, the slope of this function was the lowest of all age groups tested (Fig. 1D).

Thus, greater changes in laryngeal closure reflex threshold were produced by smaller changes in core body temperature in younger rather than older animals. That is to say, the younger the animal, the more sensitive laryngeal motoneurons were to the changes in core body temperature (Fig. 2).

Latency. Duration between stimulation and the beginning of reflex TA responses was measured oscilloscopically. Laryngeal reflex latency, being the highest at birth, markedly decreased during the first two months of postnatal life. In this study the latencies were longer at lower temperatures and shortened as body temperatures increased, showing a linear response in animals of all age groups (Table 2 and Figs. 3 and 4).

Therefore, within physiologic ranges laryngeal reflex excitability increased with increasing core body temperatures. The younger the animal, the greater the change in reflex thresholds. However, in all age groups, rate of change was greatest between 37°C and 39°C. These results indicate that laryngeal excitability is most greatly affected between 37°C and 39°C, and that this effect is greatest in newborns.

DISCUSSION

These results indicate that both the latency and the threshold of the laryngeal closure reflex decrease with a rise in body temperature, and, likewise, increase with a fall in body temperature. The change in reflex latency appears to be affected by both the velocity of axonal transmission and the velocity of synaptic transmission. It is known that the axonal conduction velocity increases as core body temperatures rise.[9] In this regard the axonal action potential is composed of a unique sequence of electrical changes, which are themselves dependent upon the ionic conductance changes produced by depolarization. In terms of the Hodgekin-Huxley equations, the rate constants for Na^+ and K^+ conductance increase threefold for every 10°C rise in temperature.[10] A study of recorded action potentials reveals that the duration of each of its phases — depolarization, potential reversal, repolarization, and hyperpolarization — occurs most rapidly as temperature increases,[11] thus contributing to a reduced latency.

TABLE 2. LATENCY OF ADDUCTOR REFLEX AT 34°C TO 41°C*

Temp C	*A*	*B*	*C*	*D*
34	22.0±2.0	19.3±2.0	19.0±0.0	18.5±0.5
35	21.2±1.6	19.2±1.6	16.5±1.0	16.7±1.1
36	20.3±1.8	18.8±1.5†	15.9±1.9	14.8±1.8
37	19.5±1.8	18.2±1.6	14.6±2.1	14.1±1.7†
38	18.6±1.8	16.8±1.3	13.3±1.8	14.0±0.7
39	17.9±1.8	15.8±1.2	12.6±2.1	13.0±1.3
40	17.2±1.7	15.3±1.2	12.3±2.8	12.5±1.5
41	16.5±1.6	14.8±1.6	12.5±2.3	13.5±0.5

*Latency in milliseconds ±SD.

At the neuromuscular junction, neuromuscular transmission is found to be slower as temperature falls because of delayed and reduced release of neurotransmitter substance. Furthermore, neurotransmitters are not released in a concentrated burst, as was the case at higher temperatures, but are dispersed over a longer period of time.[12,13] The change in time course and quantity of neurotransmitter release contributes to longer latencies at lower temperatures.

Although it appears that the effect of temperature on the speed of synaptic transmission has not been studied carefully, it is hypothesized that chemical transmission at the synapse may also be affected by changes in temperature since its presynaptic events are thought to be similar to those at the neuromuscular junction.[14] Thus, synaptic transmission may also be more rapid at a higher temperature and slower at a lower temperature.

Nevertheless, there are important differences between transmission at the neuromuscular junction and at neuronal synapses. At the neuromuscular junction, 200 to 300 vesicles of acetylcholine are released after an impulse arrives. This amount of neurotransmitter substance creates an end-plate current flow about three to four times that required to stimulate the muscle. Therefore, the normal, disease-free neuromuscular junction is said to have a high "safety factor."[15] It is unlikely that the response at the motor end-plate will be decreased by some reduction of neurotransmitter release produced by cooling. Both Katz[13] and Takeuchi[12] have shown that cooling reduces the number of responses at the motor end-plate only in a neuromuscular pre-

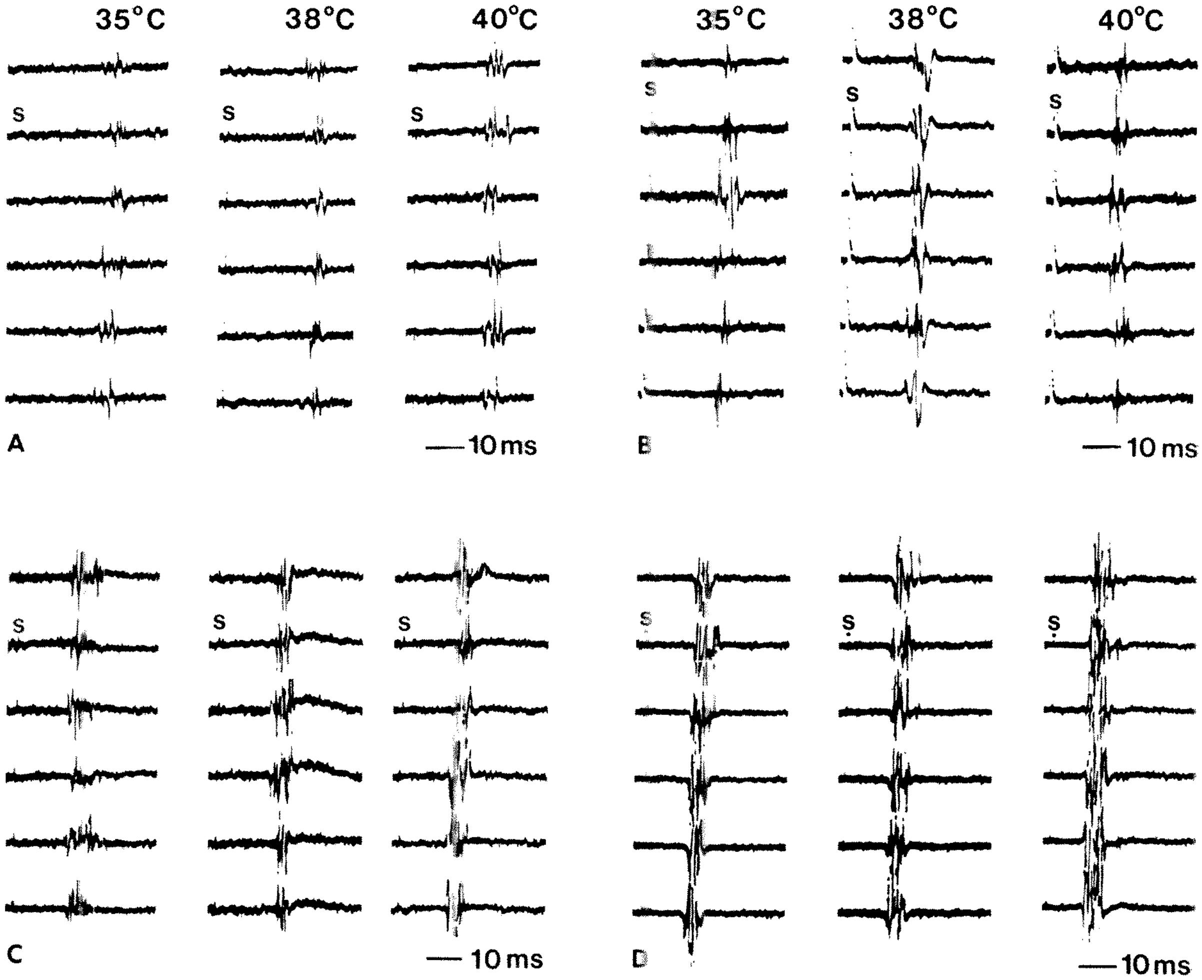

Fig. 3. Evoked adductor responses elicited by single-shock stimulation of SLN in A) 3-week-old puppies; B) 6-week-old puppies; C) 12-week-old puppies; D) Adult dogs. S -Stimulus artifact.

paration with a high Mg^{++} and low Ca^{++} concentration. This observation suggests that its threshold will only be affected by cooling under extreme experimental conditions.

On the other hand, synaptic transmission in the CNS characteristically lacks a high "safety factor," such that the threshold of a neuron may be greatly affected by temperature changes. As each action potential arrives at the synaptic knob or terminal, only one or more neurotransmitter vesicles is emptied into the synaptic cleft. This amount of neurotransmitter substance usually produces an excitatory postsynaptic potential (EPSP) of less than 1 mV, a fraction of the 10 mV or more required for the generation of an action potential. An increase in membrane potential of this magnitude requires a simultaneous discharge of ten to several hundred or more excitatory synaptic knobs.[15]

Although it appears that studies of temperature effect on CNS neurotransmitter release are largely unavailable, neuronal threshold in the spinal cord is found to decrease with temperature increase.[9] This suggests that CNS synaptic transmission may share a similar effect. Peripherally, the amount of neurotransmitter substance is shown to decrease ten times with a 19°C decrease in temperature at a sympathetic ganglion.[16] Thus, it seems possible that a synaptic knob in the CNS, which only releases one or

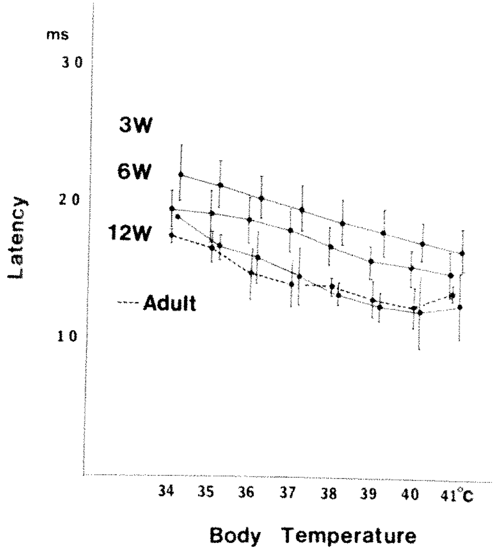

Fig. 4. Influence of body temperature on latency in four age groups. Note the linear relationship in all age groups.

more vesicles per impulse, may release fewer vesicles to none at all with cooling. Such an effect on all the excitatory synaptic knobs may result in the absence of postsynaptic action potential generation.

Consequently, it is hypothesized that action potential generation in the CNS may be more sensitive to temperature changes such that, with cooling, a stimulus of higher intensity may be required, resulting in a threshold that is raised. Similarly, it is also hypothesized that warming may increase the number of vesicles released for each impulse that arrives at the synaptic knob, such that action potentials may be generated with a weaker stimulus, lowering the threshold. Some interneurons have been shown to increase the frequency of discharge with a rise in temperature,[17] suggesting that subthreshold stimuli may generate action potentials at higher temperatures because of increased neurotransmitter release. Similarly, neurons that increase the rate of firing in response to hyperthermia have been found in the midbrain and the spinal cord.[18]

The laryngeal adductor reflex is polysynaptic; each component neuron of this reflex has a particular threshold potential that must be attained in order to generate and carry an action potential. Within this polysynaptic reflex there may be one or more neurons that define the reflex threshold. Other neurons in the chain may discharge with stimulus less than that required to attain reflex threshold. In the CNS, neurons that define the reflex threshold may thus alter the reflex threshold with temperature changes. To test this hypothesis extensive peripheral and, more important, central recordings will be necessary.

In conclusion, this study shows that both the latency and the threshold of the laryngeal closure reflex decrease with hyperthermia. The effect of temperature on latency is attributed to changes in axonal conduction and synaptic transmission velocities. Temperature-dependent changes in synaptic transmission are also proposed to be the cause of threshold changes. For example, a small temperature rise might markedly enhance the laryngeal closure reflex, which is already hyperactive during 50 to 75 days of age. Increased body temperature may thus contribute to the enhancement of transient or abnormal laryngeal closure during its period of age-related hyperexcitability. In turn, transient upper airway obstruction can induce apnea of sufficient duration as to cause sudden and unexpected death in infants.

REFERENCES

1. Bergman AB, Ray CG, Pomeroy MA, et al. Studies of the SIDS of King County, Washington, III. Epidemiology Pediatr 1972; 49:860-70.
2. Steinschneider A, Rauzzi DD. Apnea and airway obstruction during feeding and sleep. Laryngoscope 1976; 86:1359-66.
3. Naeye RL, Ladis B, Drage JS. Sudden infant death syndrome: a prospective study. Am J Dis Child 1976; 130:1207-10.
4. Naeye RL. The sudden infant death syndrome: a review of recent advances. Arch Pathol Lab Med 1977; 101:165-7.
5. Stanton AN, Scott DJ, Downham MCA. Is overheating a factor in some unexpected infant death? Lancet 1980; 1:1054-7.
6. Sasaki CT. Development of laryngeal function: etiologic significance in the sudden infant death syndrome. Laryngoscope 1979; 89:1964-82.
7. Sasaki CT, Suzuki M. Laryngeal reflex in cat, dog, and man. Arch Otolaryngol 1976; 102:400-2.
8. Bruck K. Temperature regulation in the newborn infant. Biol Neonat 1977; 3:65-119.
9. Li CL, Mathews G, Bak AF. Effect of temperature on the response of cervical vagus nerve. Exp Neurol 1977; 55:709-18.
10. Aidley DJ. The physiology of excitable cells. London: Cambridge University Press, 1971:90.
11. Klee MR, Pierau FK, Farber DS. Temperature effects on resting potential and spike parameters of cat motoneurons. Exp Brain Res 1974; 19:478-92.
12. Takeuchi N. The effect of temperature on the neuromuscular junction of the frog. Japan Physiol 1958; 8:391-404.
13. Katz B, Miledi R. The effect of temperature on the synaptic delay at the neuromuscular junction. J Physiol 1965; 181: 656-70.
14. Katz B. Nerve muscle and synapse. New York: McGraw-Hill Book Company, 1966:143-58.
15. Guyton AC. Textbook of medical physiology. Philadelphia: W B Saunders Co, 1976:148-56, 608-24.
16. Brown GL. The effect of temperature on the release of acetylcholine from sympathetic ganglion. Proceedings of Physiological Society. In: J Physiol 1954; 124:26.
17. Koizumi K, Brooks CM, Ushiyama J. Hypothermia and reaction patterns of the nervous system. Ann NY Acad Sci 1959; 80: 449-56.
18. Hensel H. Neural process in thermoregulation. Physiol Rev 1973; 53:948-1007.

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EVALUATION OF THREE CYANOACRYLATE GLUES FOR OSSICULAR RECONSTRUCTION

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We evaluated and compared the separate effects of ethyl, isobutyl, and fluoroalkyl cyanoacrylate on the promontory mucosa and surgically disarticulated incudostapedial joint in the adult cat middle ear. The animals were sacrificed at 10-, 30-, and 60-day intervals after glue application. All three cyanoacrylates elicited a chronic inflammatory response when placed directly on the promontory mucosa. The use of ethyl and isobutyl cyanoacrylate resulted in persisting discontinuity of the incudostapedial joint with erosion of the incus. Fluoroalkyl cyanoacrylate maintained incudostapedial continuity without ossicular erosion. Ethyl and isobutyl cyanoacrylate are probably not appropriate for middle ear surgery. The less toxic fluoroalkyl cyanoacrylate may be useful as an ossicular adhesive in selected cases. Our findings are further contrasted with those obtained in similar studies with methyl and butyl cyanoacrylate. The effects of each of the five cyanoacrylates are reviewed in the continuing search for a safe and effective ossicular adhesive.

INTRODUCTION

The biocompatibility and efficacy of the cyanoacrylates in otologic surgery remain controversial,[1-3] particularly when considering their long-term effects.[3,4] Since different cyanoacrylates may behave differently, a brief review of their chemistry is in order.

The remarkable adhesive qualities and unique bonding characteristics of the cyanoacrylates result from their structural configuration which allows polymerization of the monomer in the presence of a weak base such as water or alcohol. The cyanoacrylate monomers are highly fluid and have the unique ability to spread over the thin film of fluid covering most biologic tissues. Once polymerization has occurred the material becomes a hard brittle plastic. The amount of heat liberated during this exothermic reaction is small and probably biologically safe.

The different cyanoacrylates are produced by changing the alkyl subgroup of the basic molecule (Tables 1 and 2). Hardness and tensile strength decrease while flexibility increases with longer chain homologues.[5,6] The exact chemical processes by which in vivo degradation occurs are unknown. Degradation byproducts include formaldehyde, thiocyanate, carbon dioxide, and water. Short chained compounds are eliminated more rapidly than longer chained homologues, and branched chain compounds are eliminated more rapidly than those with straight chains.[5,6]

Methyl cyanoacrylate (MC) is unsuitable for clinical use. It causes severe tissue necrosis in the middle ear, and there is evidence to suggest that it is toxic to the labyrinth.[1,7-9] The efficacy of butyl (BC) and isobutyl (IC) cyanoacrylate as adhesives for otologic surgery has been evaluated by several investigators[1,2,10-14] with no agreement as to the overall suitability and safety of either compound. For example, Siedentop[1] recently declared Histoacryl (BC) to be "harmless to middle and inner ear structures" and "safe for use in human middle ear surgery," while almost simultaneously Heumann and Steinbach[2] concluded that the same substance "be used with extreme care and in small amounts" and that it was "extremely dangerous to use this adhesive near the labyrinthine capsule [for example, on the footplate]." Conflicting results such as these may be due, in part, to the use of different animal models such as dogs,[1] baboons,[1] rabbits,[2] monkeys,[11] guinea pigs,[10] and cats.[14] There are no published reports on the potential usefulness of either ethyl (EC) or fluoroalkyl (FC) cyanoacrylate in middle ear surgery.

The purpose of this study was to evaluate and compare the effects of EC, IC, and FC as adhesives for ossicular reconstruction in the cat. We purposely omitted MC and BC from our study: MC because of its well-documented propensity to cause severe tissue necrosis, and BC because it has already been widely investigated for this purpose.[1,2,10-14]

METHOD

Nine middle ear procedures were performed on seven adult cats using standard sterile techniques. The animals were anesthetized with intramuscular ketamine hydrochloride (20 mg/kg) and intraperitoneal sodium pentobarbital (10 mg/kg). The tympanic bulla was approached through a ventral paramedian neck incision and opened to expose the oval and round windows, cochlear promontory, and ossicular chain. The tympanic membrane was not disturbed. The incudostapedial joint was interrupted with a joint knife and joint separation confirmed by lateral traction on the handle of the malleus.

Using a specially developed glass micropipette applicator, a small aliquot (approximately 1-2 μl) of cyanoacrylate was placed

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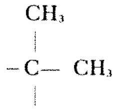
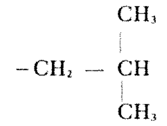
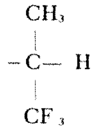
TABLE 1. ALKYL SUBGROUPS USED TO PRODUCE DIFFERENT CYANOACRYLATES

Subgroup	*Structure*
Methyl	$-CH_3$
Ethyl	$-CH_2-CH_3$
Butyl	 $-\overset{CH_3}{\overset{\mid}{\underset{\underset{CH_3}{\mid}}{C}}}-CH_3$
Isobutyl	 $-CH_2-\overset{CH_3}{\overset{\mid}{\underset{\underset{CH_3}{\mid}}{CH}}}$
Fluoroalkyl	 $-\overset{CH_3}{\overset{\mid}{\underset{\underset{CF_3}{\mid}}{C}}}-H$

between the capitulum of the stapes and the lenticular process of the incus. An additional single large drop of glue was placed on the promontory mucosa. The incision was closed with interrupted sutures.

Ethyl cyanoacrylate and FC were each used in the middle ears of three cats; the six animals were sacrificed at 10-day, 30-day, and 60-day intervals. Isobutyl cyanoacrylate was used in the middle ears of two additional cats which were sacrificed 30 and 60 days after surgery. As a control, one cat's ossicular chain was disarticulated but no glue used to reapproximate the incudostapedial joint.

At the end of the designated survival period the middle ear was reopened and the ossicular chain inspected and palpated for continuity and mobility. The middle ear mucosa was examined and a piece of promontory mucosa (from where the drop of glue had been placed) was excised for histologic examination. The stapes footplate was exposed, the stapedial tendon divided, and the stapes and incus removed en bloc for histologic examination.

RESULTS

All three cyanoacrylates caused varying degrees of inflammation and fibrosis in the middle ear mucosa. The chronic inflammatory response elicited by each glue was particularly evident in the mucosal specimens from the promontory where the additional single drop of glue had been placed. Histologic examination showed increased vascularity, lymphocytic infiltration, fibrous proliferation, and, occasionally, granuloma formation. Polymorphonuclear leukocytes were prominent only in the mucosal specimen from the one animal which developed an acute otitis media (EC, 10-day survival). The intensity of the inflammatory process (measured by the amount and degree of cellular infiltration and fibrous thickening) did not appear to be correlated with a specific glue or the length of glue-mucosa contact time. The effect of the different cyanoacrylates on the incus and stapes varied from relatively benign to destructive.

Ethyl Cyanoacrylate. The 10-day animal developed acute otitis media with tympanic membrane perforation, a markedly hyperemic middle ear mucosa, and erosion of the incus and stapes. In the 30-day animal the promontory mucosa was hyperemic and thickened with a small remaining remnant of polymerized EC. Ossicular continuity was maintained with a thick fibrous cocoon enveloping the incudostapedial joint. There was no evidence of ossicular erosion. In the 60-day animal, the promontory mucosa was mildly inflamed and thickened, but the remainder of the middle ear mucosa was normal. A tiny remnant of polymerized EC remained on the promontory. There was no ossicular continuity: the long process of the incus was eroded (Fig. 1) almost to the body of the incus and the stapes superstructure was absent. A moderate amount of thickened mucosa surrounded the body of the incus.

TABLE 2. CYANOACRYLATES USED IN CLINICAL TRIALS AND EXPERIMENTAL SURGERY

Generic Name	*Proprietary Name*
Methyl 2-cyanoacrylate	Eastman Kodak 910*
Ethyl cyanoacrylate	Aaron Alpha†
2-cyano-butyl-acrylate	Histoacryl‡
Isobutyl cyanoacrylate	Bucrylate§
Fluoroalkyl cyanoacrylate	MBR 4197R‖

*Eastman Kodak, Rochester, NY.
†Toayosei Chemical Industry Company, Tokyo.
‡B. Braunmelsengen, Melsengen, W Germany.
§Ethicon Inc, Somerville, NJ.
‖3M Company, St. Paul.

Isobutyl Cyanoacrylate. A considerable amount of polymerized IC remained on the promontory mucosa of both the 30- and 60-day animals with no evidence of active resorption or encapsulation. The promontory mucosa was markedly thickened and polypoid and the inflammatory process appeared to extend well beyond the area where the drop of glue had been placed. There was an ossicular discontinuity with erosion of the lenticular and long process of the incus in both instances. The ossicular remnants were surrounded with polypoid mucosa and fibrous adhesions.

Fluoroalkyl Cyanoacrylate. The findings were remarkedly similar in the 10-, 30-, and 60-day animals. Polymerized FC was present on the promontory mucosa in all three instances with no evidence of active resorption or encapsulation of the glue. The promontory mucosa beneath the glue was moderately thickened and polypoid in appearance. Mucosa immediately adjacent to the glue was only slightly inflamed and thickened, while the rest of the middle ear mucosa appeared normal. Extension of the inflammatory process beyond the immediate area of the glue placement was more pronounced in the 60-day animal. Ossicular continuity was preserved in all three cats, and motion of the malleus was readily transmitted to the stapes in each case. The incudostapedial joint was surrounded by a fibrous cocoon which provided firm continuity between the two ossicles (Fig. 2). There was no evidence of erosion of the incus or stapes.

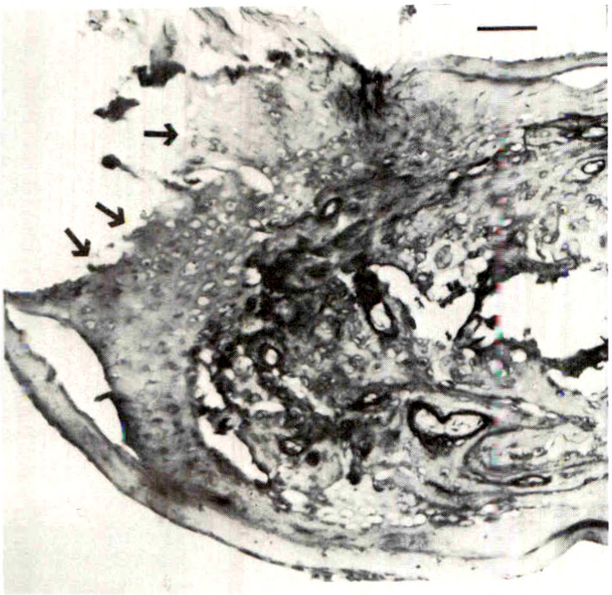


Fig. 1. Light-field photomicrograph of the long process of cat incus showing bony erosion (arrows) following application of ethyl cyanoacrylate to the surgically disarticulated incudostapedial joint. Sixty days survival. (Bar = 50 μ)

DISCUSSION

Fluoroalkyl cyanoacrylate appears to hold the most promise as a useful and relatively nontoxic ossicular adhesive of the three glues evaluated in this study. A minute quantity of fluoralkyl cyanoacrylate provided ossicular continuity without bone erosion or overt tissue necrosis. Although no symptoms of labyrinthine dysfunction were noted in this series, additional specific animal experimentation is necessary to assess potential labyrinthine toxicity.

None of the three cyanoacrylates was completely resorbed from the promontory mucosa at 60 days. The remnants of polymerized EC were significantly smaller than those of IC and FC at comparable survival times. This is consistent with the observation[1,5] that short chain homologues are more rapidly eliminated than long chain compounds. The inflammatory response to the single drop of glue on the promontory mucosa was initially quite localized, but spread to involve the adjacent mucosal surface with increasing survival time. The intensity of the initial inflammatory response appeared to be directly related to the amount (but not type) of glue used in each experiment. It is interesting to speculate whether the inflammatory process would persist or subside once the polymerized glue had been completely resorbed.

Erosion of the incus and stapes did not appear to reflect or correlate with the intensity of the promontory mucosal response. FC was the only adhesive in this study that preserved incudostapedial integrity (Fig. 2) in all three animals; EC and IC were ineffective ossicular adhesives causing incudostapedial discontinuity and erosion (Fig. 1).

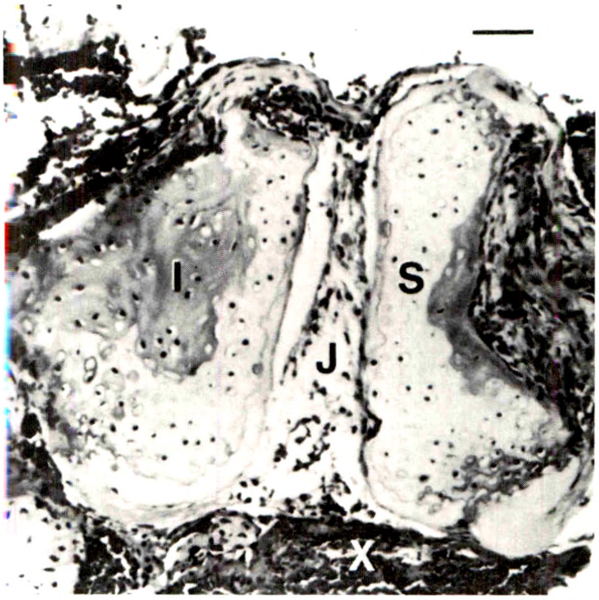


Fig. 2. Light-field photomicrograph of an intact incudostapedial joint 60 days following application of a minute quantity of fluoroalkyl cyanoacrylate into the surgically disarticulated cat incudostapedial joint. Note the absence of bony erosion of either the incus (I) or stapes (S). An inflammatory response is noted in the joint space (J) and surrounding capsule (X). (Bar = 50 μ)

Characteristics of the ideal tissue adhesive include such properties as noncarcinogenicity, minimal inflammatory response, effective and durable bond on moist tissue surfaces, and biodegradability.[1] None of the five cyanoacrylates (Table 2) fulfills these criteria, although only MC can be definitely excluded from the list because of excessive tissue necrosis and a possible carcinogenic effect.[1] Recently published conflicting reports[1,2] on the efficacy and safety of Histoacryl based upon animal middle ear studies highlight the need for careful and extensive evaluation of each of the cyanoacrylates before their recommendation for long-term clinical use. Middle ear evaluation should include both acute and prolonged survival histologic studies in at least two different animal species since, at least in the acute phase, there appears to be a distinct and often contradictory interanimal and interspecies variation.[10,11] Labyrinthine toxicity studies should include not only anatomic integrity (eg, intact footplate) but also prolonged survival ultrastructural and neurophysiologic evaluation of the sensory neuroepithelium of the cochlea and vestibular labyrinth. In the absence of such studies we can only agree with Portmann's decision[3,4] to abandon the use of cyanoacrylates in human middle ear surgery at this time.

ACKNOWLEDGMENTS — The authors thank Roger Coble and Aaron Smith for their technical assistance.

REFERENCES

1. Siedentop KH. Tissue adhesive Histoacryl (2-cyano-butyl-acrylate) in experimental middle ear surgery. Am J Otol 1980; 2: 77-87.

2. Heumann H, Steinbach E. The effects of an adhesive in the middle ear. Arch Otolaryngol 1980; 106:734-7.

3. Portmann M. The ear and temporal bone. New York: Masson Publishing, USA, Inc, 1979.

4. Donaldson JA. Letter to the editor. Am J Otol 1981; 2: 410.

5. Coover HW, McIntire JM. The chemistry of cyanoacrylate adhesives. In: Matsumoto T, ed. Tissue adhesives in surgery. New York: Medical Examination Publishing Co, 1972.

6. Smith DC. Lutes, glues, cements and adhesives in medicine and dentistry. BioMed Eng 1968; 146:203-13.

7. Guildford FR, Shaver EF, Halbert B. Incus repositioning in dogs. Arch Otolaryngol 1966; 84:316-9.

8. McKelvie P. A trial of adhesives in reconstructive middle ear surgery. J Laryngol Otol 1969; 83:1105-9.

9. Kerr AG, Smyth GDL. Bucrylate (isobutyl cyanoacrylate) as an ossicular adhesive. Arch Otolaryngol 1971; 94:129-31.

10. Tabb HG. Ossicular repositioning with bone glue in tympanoplasty. Trans Pac Coast Otoophthalmol Soc Annu Meet 1968; 49:51-5.

11. Kaufman RS. The use of tissue adhesive isobutyl cyanacrylate and topical steroid (0.1 percent dexamethasone) in experimental tympanoplasty. Laryngoscope 1974; 84:793-804.

12. Decher H. Die Acrylatpexie bei der Tympanoplastik. HNO 1971; 19:239-41.

13. Schneider EA. Experiences with tissue adhesives in middle ear operations. ORL 1972; 34:227-39.

14. Smyth GDL, Kerr AG. Histoacryl (butyl-cyanoacrylate) as an ossicular adhesive. J Laryngol Otol 1974; 38:539-42.

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SECOND INTERNATIONAL TINNITUS SEMINAR

The Second International Tinnitus Seminar will be held June 10-11,1983, at the New York Hilton in New York. For further information contact Abraham Shulman, MD, Chairman, or Barbara Goldstein, PhD, Coordinator, Division of Otolaryngology, SUNY Downstate Medical Center, Box 40, 450 Clarkson Avenue, Brooklyn, New York 11203; (212) 270-1638.

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TEMPORAL BONE HISTOPATHOLOGY ASSOCIATED WITH OCCLUSION OF VERTEBROBASILAR ARTERIES

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We have presented the histological findings in the inner ear of a patient who experienced occlusion of the vertebral and basilar arteries 17 days before death. A large infarction was observed in the medulla and pons on the right side. There was severe degenerative change in the right membranous labyrinth as well as in the right cochlear and vestibular nerves, which was presumably caused by ischemia from occlusion of the right labyrinthine artery. The organ of Corti and sensory epithelia of the vestibular labyrinth showed the most advanced state of degeneration. The histopathological appearance was similar to that observed in the subacute stage following obstruction of the labyrinthine arteries in animal experiments.

INTRODUCTION

Several authors have studied the histopathological changes of the inner ear caused by experimental interruption of the labyrinthine arteries of animals. Complete occlusion caused severe degeneration of the membranous labyrinth[1,2] while microembolization of the cochlear vessels caused patchy isolated areas of necrosis.[3]

There have been several human temporal bone reports in which the major histopathology was thought to be caused by interruption of vascular supply to the inner ear.[4-6] Some of these temporal bones were from patients who underwent surgery for removal of an acoustic tumor or for vestibular nerve section and the pathological findings were obviously surgically induced.

The purpose of this paper is to report the histopathology of the temporal bones from a patient who experienced pathological occlusion of the basilar artery and probably also the right anterior inferior cerebellar artery.

CASE HISTORY

Our patient was a male known to have von Recklinghausen disease. His two daughters and one son have cutaneous manifestations of the disease and one maternal cousin has the disease also with no neurological involvement. At age 56 he underwent left trigeminal neurotomy to relieve left facial pain of 12 years' duration. At that time he demonstrated bilateral partial foot-drop and terminal tremor on the finger-nose test. There was also horizontal nystagmus on right and left lateral gaze. A pneumoencephalogram showed a slight widening of the lateral third and fourth ventricles consistent with mild atrophic changes of the cerebellum. A myelogram was suggestive of an intraspinal neurofibroma in the L4-5 area.

At the age of 60 examination again showed mild cerebellar signs and nystagmus on lateral gaze. An audiogram showed hearing to be normal for his age. Speech discrimination scores were 100% in the right and 88% in the left ear. Tone decay was negative at 500 and 2000 Hz in both ears (Fig. 1).

At age 65 he experienced vomiting, bifrontal headache, and light-headedness without vertigo. The following day he was dysarthric and unable to walk, lethargic but easily arousable, had hiccups, and his head deviated to the right. Horizontal eye movements were diminished, more to the right. He had horizontal nystagmus on lateral gaze which was the same kind of nystagmus seen on previous examination. There was left facial palsy of the central type. His tongue was deviated to the right. Although no audiogram was taken, he noted decreased hearing on the right. Cold, touch, and pin sensation were felt less on the left; there was left hemiparesis. The following day his eyes were deviated to the left. He became deeply comatose five days later. A CT scan at that time showed an infarction of the right pontine tegmentum. Ice water caloric tests showed vertical nystagmus on both sides which were interpreted to support the diagnosis of brainstem infarction. He died 17 days after the onset of symptoms. An autopsy was performed and both temporal bones were removed for histological study. Postmortem time was 12 hours.

AUTOPSY FINDINGS

There is an aneurysm of the left vertebral artery which shows atherosclerotic walls and widespread

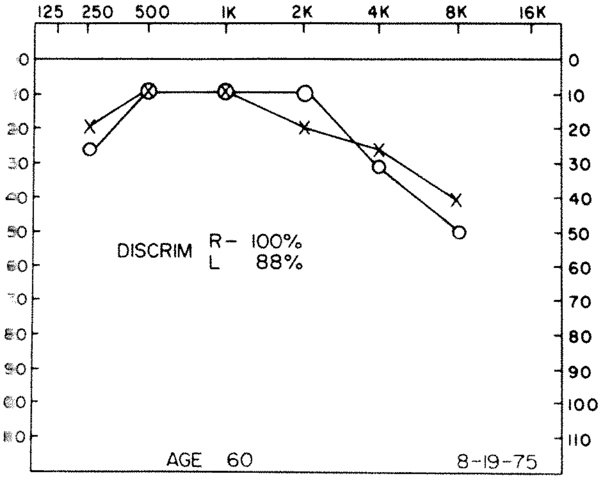

Fig. 1. Audiogram obtained four years before death. Speech discrimination scores were 100% in the right and 88% in the left ear.

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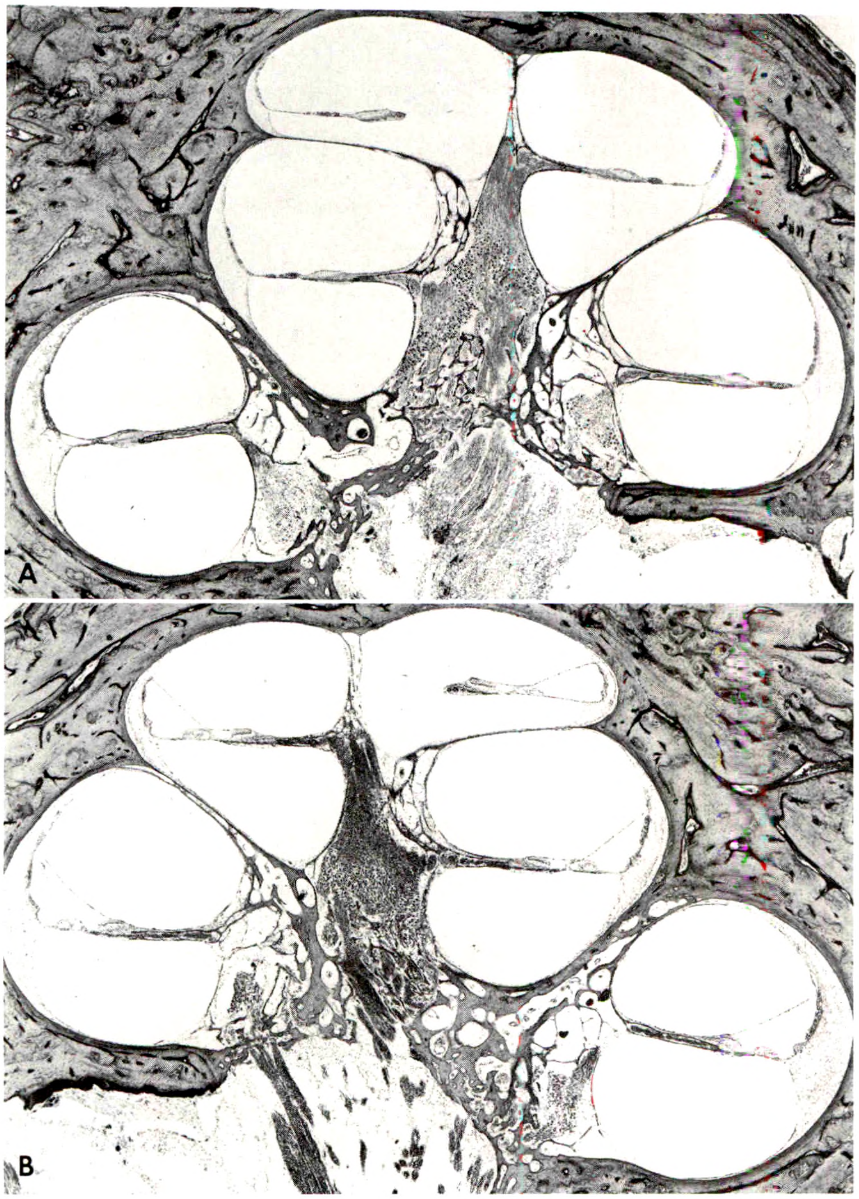

Fig. 2. A) Right cochlea showing collapse of the cochlear duct and degeneration of the cochlear nerve. The spiral ganglion cell population is nearly normal except for the basal area of the cochlear duct. B) Left cochlea showing patchy atrophy of the stria vascularis and 50 to 80% loss of the spiral ganglion cells in the basal turn.

destruction of the media. The lumen is largely occluded by an old thrombus; however, it appears wide enough to allow normal blood flow.

The right vertebral artery shows severe atherosclerotic changes with an organized thrombus that occludes the lumen. Within the thrombus are many recanalized channels lined with endothelium.

The basilar artery shows very severe atherosclerosis and an adherent recent thrombus, the appearance of which is consistent with the duration of the terminal illness (17 days).

In the anterolateral part of the medulla and in the basis pontis on the right there is a large cavitated infarction containing necrotic tissue and numerous macrophages. Periventricular demyelinated plaques are seen in both hemispheres and brainstem consistent with multiple sclerosis. There are multiple small infarcts of varying age in the cerebellum, pontocerebellar connections, hemispheric white matter and basal ganglia.

Additional autopsy findings include extensive cutaneous neurofibromata, multiple café au lait spots and a plexiform neuroma in the L4 and 5 region of the spine.

HISTOPATHOLOGY

Right Ear. There is a mass of keratin and blood in the external auditory canal. The ossicles and the tympanic membrane are intact. The mucous membrane of the middle ear and mastoid are well preserved. The mastoid is well developed. The bony labyrinth appears normal. Normal-appearing ganglion cells are found along the course of the tympanic plexus and lesser superficial petrosal nerve.

There is a severe degenerative change involving the membranous labyrinth as well as the cochlear and vestibular nerves. The organ of Corti appears

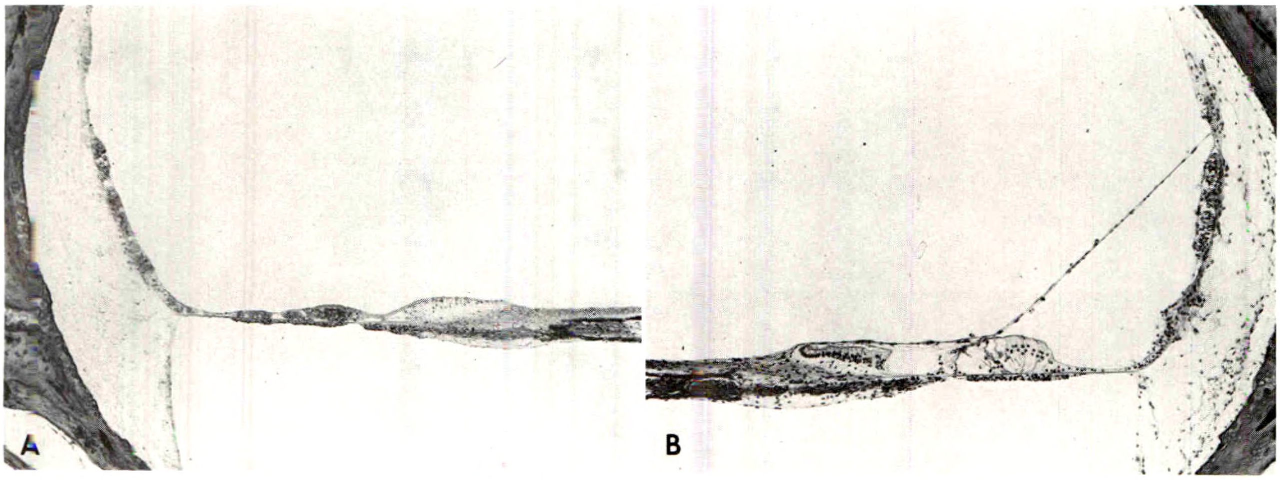

Fig. 3. A) High magnification view of the cochlear duct in the middle turn shown in Fig. 2A. The organ of Corti is atrophied. Loss of cellularity is remarkable in the spiral ligament, stria vascularis and spiral limbus. B) High magnification view of the cochlear duct in the middle turn shown in Fig. 2B. Note normal appearance of the cochlear duct.

as a mound of atrophied acidophilic amorphous tissue. No cell outlines are observed. In addition, there is loss of cellularity of the spiral ligament, stria vascularis, spiral limbus and Reissner membrane, most severe in the apical 15 mm of the cochlea. Reissner's membrane is depressed onto the organ of Corti throughout the cochlea (Figs. 2 and 3). The spiral ganglion cells appear as round pink granular bodies with or without faintly stained nuclei (Fig. 4). The population of these degenerating spiral ganglion cells is reduced to 50% or less in the basal 17 mm of the cochlea. In the remainder of the cochlea the population appears normal (Fig. 2). The cochlear nerve shows degenerative changes similar to those observed in the cochlea.

The cristae and maculae are in an advanced state of degeneration. The supporting tissues show degenerating cells with faint outlines and absent nuclei. The sensory epithelia of the cristae and maculae consist of a layer of similarly degenerating tissue

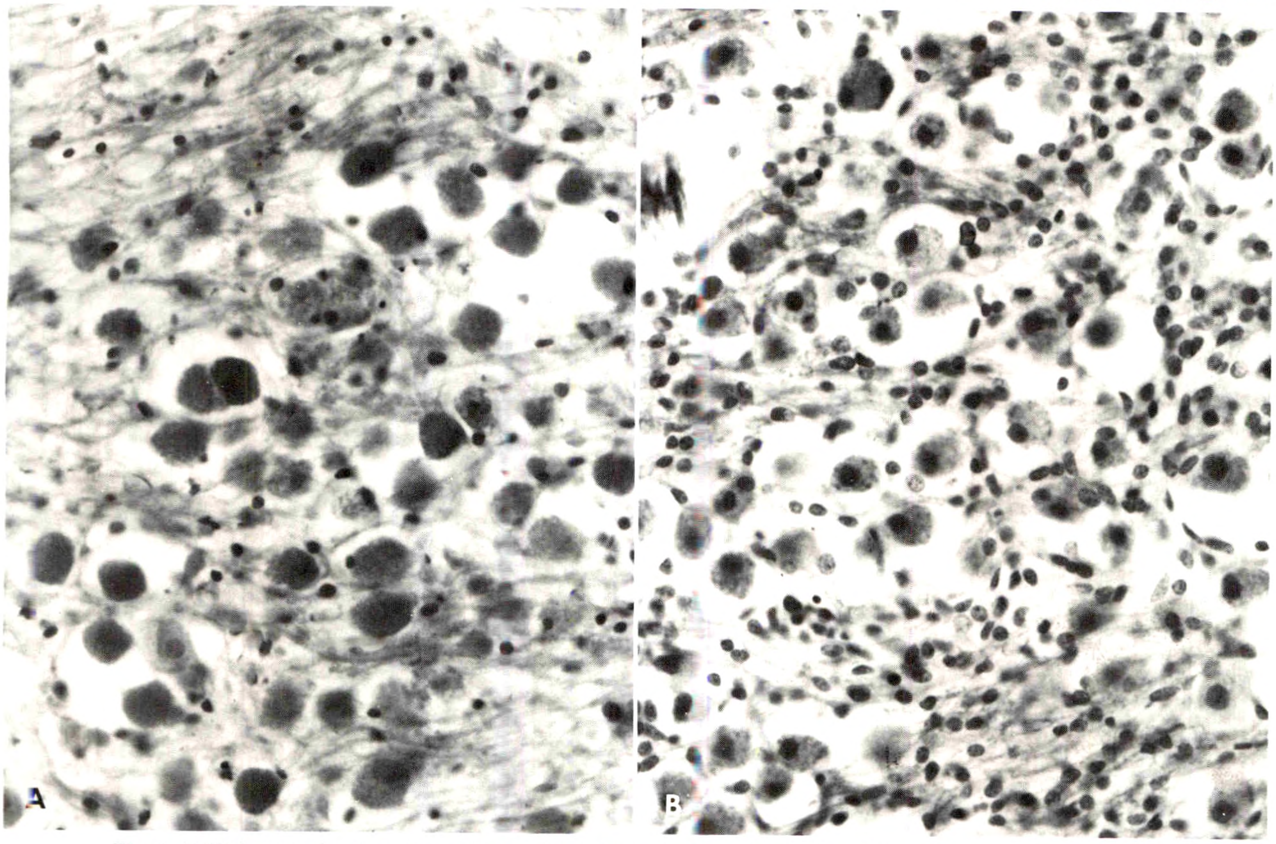

Fig. 4. A) High magnification view of the spiral ganglion cells shown in Fig. 2A. Cell nuclei are missing or stained faintly. B) High magnification view of the spiral ganglion cells shown in Fig. 2B. Cell nuclei are observed in all ganglion cells.

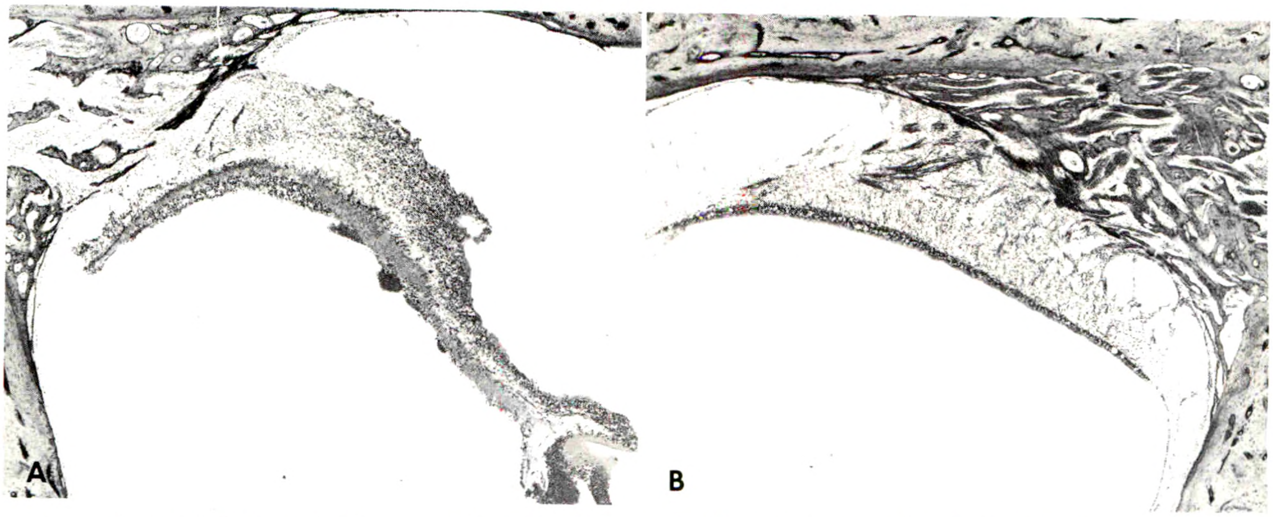

Fig. 5. A) Right utricle shows severely atrophied sensory epithelium and collapsed utricular wall. Note severely atrophied branch of the superior vestibular nerve. B) Normal appearance of the left utricle.

separated from the underlying stroma. There is collapse of the walls of the utricle as well as the superior and lateral semicircular canals (Fig. 5). There are scattered collections of erythrocytes in both the perilymphatic and endolymphatic spaces of the superior and lateral semicircular canals.

The superior and inferior vestibular nerves are atrophic and most of the Scarpa ganglion cells are missing, especially in the superior division of the vestibular nerve. The number of neurons determined by the method introduced by Richter[7] is 3,883 (Fig. 6); normal for the patient's age is 12,000 to 17,000.[7]

The facial nerve trunk appears atrophic in the internal auditory canal. The geniculate ganglion cells show similar degenerative changes. Their population is one half of the opposite ear (1,470 cells). The average number of cells was reported to be 2,129 with a range of 1,462 to 3,682.[8]

The epithelium of the endolymphatic sac is well preserved.

The labyrinthine artery appears patent in the distal end of the internal auditory canal; however, its proximal portion as well as the anterior inferior cerebellar artery is not observed in this temporal bone specimen.

Left Ear. The tympanic membrane, ossicles, middle ear and mastoid appear normal. The bony labyrinth is normal. There is scattered loss of hair cells in the organ of Corti particularly in the basal turn. The stria vascularis shows patchy atrophy more remarkable in the apical region of the cochlea. There is 50 to 80% loss of cochlear neurons in the basal turn and normal population in the rest of

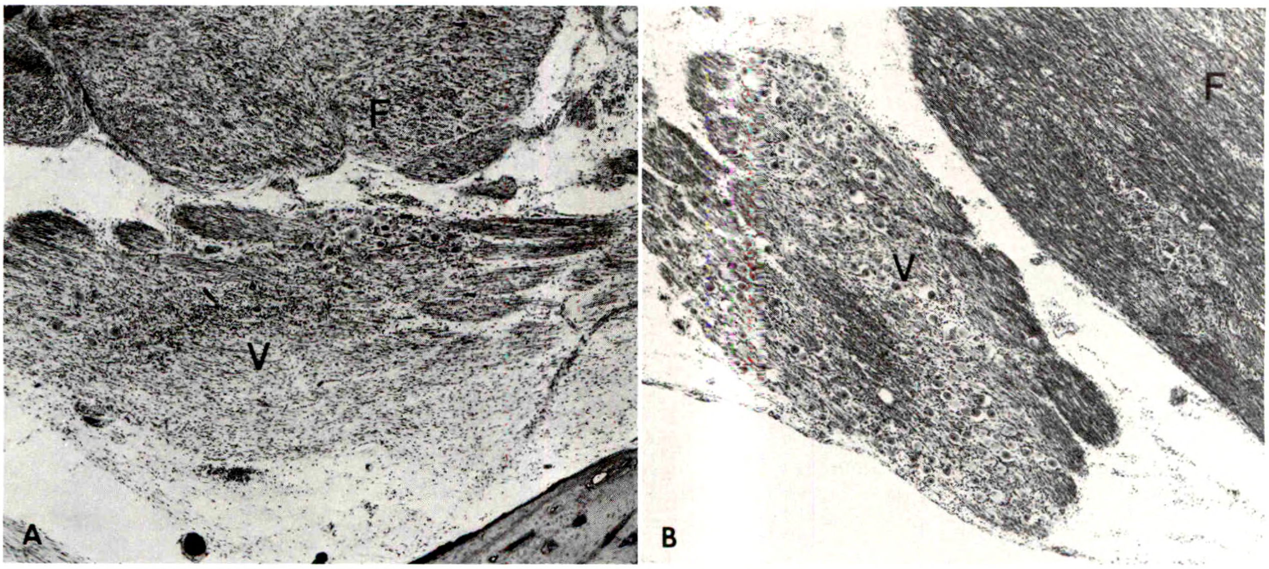

Fig. 6. A) Lower half of the picture shows the atrophic superior vestibular nerve (V) and reduced population of Scarpa ganglion cells. The facial nerve (F) appears atrophic in the upper half of the picture. B) Normal appearance of the facial (F) and the superior vestibular nerve (V).

the cochlear duct (Figs. 2-4). The cochlear nerve appears normal.

The utricular and saccular maculae and the cristae are well preserved (Fig. 5). The vestibular and facial nerves appear normal. The numbers of Scarpa and geniculate ganglion cells are 17,132 and 2,829, respectively (Fig. 6).

DISCUSSION

Although vascular connections of arteriolar size have been shown to exist between the membranous structures and the bony labyrinthine capsule of the labyrinth,[9] it is generally accepted that the major blood supply to the inner ear is provided by the labyrinthine artery. Previous studies have shown that the labyrinthine arteries may derive from the basilar artery[10] or from the anterior inferior cerebellar artery.[11,12] Several cases of severe unilateral sensorineural hearing loss occurring in association with occlusion of the basilar artery have been reported in the literature.[13] A vascular disturbance in the basilar artery may cause ischemic necrosis of the ascending auditory pathway in the brainstem. However, in the type of hearing loss which will be discussed here, the lesion is expected in the peripheral cochlear end-organ because of its unilateral involvement. A review of the literature has failed to reveal any reports of temporal bone pathology following occlusion of the basilar arteries.

The autopsy of this subject showed a large infarction in the medulla and pons on the right side. In addition, the right membranous labyrinth and associated nerves showed severe degenerative changes. The presence of the lesion in the pons indicated that the region of supply of the basilar artery was involved in addition to that of the right vertebral artery. In view of this evidence of occlusion of the basilar artery and unilateral severe degenerative changes in the inner ear, it is probable that the right labyrinthine artery was occluded also, whether it branched from the basilar artery or anterior inferior cerebellar artery. The presence of numerous macrophages in the infarcted area is consistent with a recent lesion (2 to 3 weeks), indicating that it must have occurred during the patient's last admission to the hospital.

The histopathological changes in this ear are similar to those observed after obstruction of the labyrinthine arteries in animal experiments.[1] The sensory hair cells were reported to be the most vulnerable with pyknosis of hair cell nuclei being visible within one hour after arterial obstruction. In one week the hair cells disappeared and the membranous labyrinth was severely degenerated. After one month the inner ears were partially filled with fibrous tissue and new bone. The absence of new bone or fibroblasts in the membranous labyrinth of the temporal bones of this human case indicates a recent occlusion of the labyrinthine blood flow.

Another striking finding in the present case was the severe loss of Scarpa ganglion cells in the involved ear. The degree of degenerative change of the Scarpa ganglion cells is more severe than that of the spiral ganglion cells. In the animal studies Scarpa ganglion cells were less involved than spiral ganglion cells after obstruction of the labyrinthine arteries.[1] Although there is nothing in the history to determine what caused the loss of Scarpa ganglion cells, it is probable that diminution of Scarpa ganglion occurred prior to the recent vascular disturbance.

The epithelium of the endolymphatic sac and mucous membrane of the middle ear appeared normal. In addition, intact ganglion cells were observed in the tympanic plexus and lesser superficial petrosal nerve which are supplied by branches of the inferior tympanic artery and the anterior tympanic artery. The histological evidence of well-preserved tissue in the regions supplied by the external carotid artery preclude the possibility that the inner ear changes are due to postmortem autolysis.

Lindsay and Hemenway[4] reported a human temporal bone in which atrophy of the superior division of the vestibular nerve and associated sense organs were attributed to the occlusion of the anterior vestibular artery. However, vascular occlusion was not demonstrated. Belal et al[5] published a temporal bone case report in which the anterior vestibular artery was occluded following middle fossa vestibular nerve section. In this case the hair cells of the utricular macula appeared intact which is in variance to animal studies which show sensory cells to be most vulnerable to obstruction of the labyrinthine artery. In another study, House and Belal[6] found that translabyrinthine removal of tumor and its attendant interference with blood supply caused abundant hemorrhage. In animal studies venous obstruction led to hemorrhage while arterial obstruction did not.[1,2,14] We would expect that both arterial and venous disturbances might occur in the temporal bone following surgery in the internal auditory canal.

In summary, we have presented the histological findings in the inner ears of a patient who experienced occlusion of the vertebral and basilar arteries 17 days before death. The right membranous labyrinth shows advanced degeneration presumably caused by ischemia from occlusion of the right labyrinthine artery. No hemorrhages are seen and there is no evidence of a host reponse to this severe state of labyrinthine necrosis.

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REFERENCES

1. Kimura RS, Perlman HB. Arterial obstruction of the labyrinth. Ann Otol Rhinol Laryngol 1958; 67:5-40.

2. Perlman HB, Kimura RS, Fernandez C. Experiments on temporary obstruction of the internal auditory artery. Laryngoscope 1959; 69:591-613.

3. Igarashi M, Alford BR, Konishi S, Shaver EF, Guilford FR. Functional and histopathological correlations after microembolism of the peripheral labyrinthine artery in the dog. Laryngoscope 1969; 79:603-23.

4. Lindsay J, Hemenway W. Postural vertigo due to unilateral sudden partial loss of vestibular function. Ann Otol Rhinol Laryngol 1956; 65:692-706.

5. Belal A Jr, Linthicum FH Jr, House WF. Middle fossa vestibular nerve section. A histopathological report. Am J Otol 1979; 1:72-9.

6. House WF, Belal A Jr. Translabyrinthine surgery. Anatomy and pathology. Am J Otol 1980; 1:189-98.

7. Richter E. Quantitative study of human Scarpa's ganglion and vestibular sensory epithelia. Acta Otolaryngol (Stockh) 1980; 90:199-208.

8. Van Buskirk C. The seventh nerve complex. J Comp Neurol 1945, 82:303-33.

9. Hansen CC. Vascular anatomy of the human temporal bone. I. Anastomoses between the membranous labyrinth and its bony capsule. Arch Otorhinolaryngol 1971; 200:83-98.

10. Walker EA Jr. The vertebro-basilar arterial system and internal auditory angiography. Laryngoscope 1965; 75:369-407.

11. Nabeya D. A study in the comparative anatomy of the blood-vascular system of the internal ear in mammalia and in homo (Japanese). Acta Sholae Med Univ Imp Kyoto 1923; 6:1-132.

12. Mazzoni A. Internal auditory canal arterial relations at the porus acusticus. Ann Otol Rhinol Laryngol 1969; 78:797-814.

13. Williams D, Wilson TG. The diagnosis of the major and minor syndromes of basilar insufficiency. Brain 1962; 85:741-74.

14. Kimura RS, Perlman HB. Extensive venous obstruction of the labyrinth. A. Cochlear change. Ann Otol Rhinol Laryngol 1956; 65:332-51.

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THE 16TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEAD AND NECK RADIOLOGY

The 16th Annual Meeting of the American Society of Head and Neck Radiology will be held May 26-29, 1983, at the Boston Marriott Hotel. Inquiries should be directed to Barbara Carter, MD, North East Medical Center, 171 Harrison Avenue, Boston, MA 02111.

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DIFFERENTIAL FACIAL NERVE FUNCTION IN TUMORS OF THE INTERNAL AUDITORY MEATUS

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Fifty-five consecutive cases of neoplastic involvement of the internal auditory meatus resulting in ipsilateral retrocochlear auditory dysfunction were reviewed. The majority of these tumors (89%) were solitary schwannomas of the eighth nerve. Eleven percent were other tumors. Preoperative facial paralysis was unusual in eighth nerve schwannomas (6.1%) and much more common in other tumors (66.6%). These data tend to suggest that facial paralysis preoperatively increases the probability that the tumor is other than an eighth nerve schwannoma. Furthermore, facial paralysis resulting from an eighth nerve schwannoma indicates a poorer prognosis for ultimate facial nerve function. The small numbers in this series, though far from conclusive, suggest that normally functioning facial nerves may be infiltrated by eighth nerve schwannomas. Failure of eventual recovery of facial nerve function in the postoperative period may suggest tumor infiltration.

INTRODUCTION

Brackmann and Bartels,[1] in analyzing 1,354 cerebellopontine angle tumors, found approximately 10% to be lesions other than eighth nerve schwannomas. Their observations and those made earlier by Sundaresan et al,[2] describing three vascular lesions of the internal auditory meatus, suggest that facial paresis in lesions of the internal auditory meatus may have diagnostic implications as to the tissue type of that lesion.

The purpose of this paper is to present our experiences with 55 consecutive surgically confirmed tumors involving the internal auditory meatus and their apparent differential effect upon the ipsilateral facial nerve.

METHODS

Preoperative, operative and postoperative neurotologic and neurosurgical observations of 55 consecutive patients with surgically confirmed tumors involving the internal auditory meatus and presenting with ipsilateral retrocochlear hearing loss were studied. One illustrative case is presented. Statistical analysis of the distribution of results was analyzed by the Fisher Exact Probability Test.

CASE REPORT

A 31-year-old male became aware of a hearing loss in the right ear in March 1975 when, while lying on his left side, he had difficulty hearing his wife's voice. He had no other symptoms at that time. Physical examination was normal. Audiometry in August 1975 showed the patient to have a right-sided mild-to-moderate sensorineural loss with a pure tone average of 33 dB, a phonemically balanced word maximum score of 76% and absent acoustic reflexes along the afferent limb of the reflex arc; the efferent limb of the reflex arc bilaterally was normal. The Suprathreshold Adaptation Test (STAT) and Bekesy Comfortable Loudness Test (BCL) were negative. Electronystagmography showed a profound unilateral vestibular weakness on the right, moderately intense left-beating spontaneous nystagmus, left horizontal gaze nystagmus, slight predominance of the left-beating optokinetic nystagmus, and left-beating caloric directional preponderance. Tomograms of the internal auditory meati and a CT scan were normal. A posterior fossa myelogram failed to fill the right internal auditory meatus but did not clearly circumscribe a mass lesion.

During the ensuing 14 months, the auditory sensitivity of the right ear remained stable; however, there was fluctuation of speech discrimination, occasionally with "roll-over," and fluctuation of the stapedius reflex along the afferent limb of the reflex arc.

The patient was seen 16 months later and a gradually progressive hearing loss was documented, this time with a pure tone average of 62 dB and 0% speech intelligibility function. STAT was positive and Bekesy threshold audiometry showed a type III pattern. No afferent stapedius reflex and no auditory brainstem responses were elicited from the right ear (Fig. 1).

The patient was encouraged to undergo further evaluation; he temporarily refused until eight months later when he suffered a sudden right lower motor neuron facial paresis. The right facial paresis involved all branches of the facial nerve with an estimated loss of approximately 50% of function. Polytomography of the fallopian canal on the right was normal; however, the right internal auditory meatus was enlarged by 2 mm at the porus with a suggestion of erosion of the canal floor. Posterior fossa myelography demonstrated nonfilling of the right internal auditory meatus with a filling defect in the cerebellopontine angle of approximately 1½ cm. A postinfusion CT scan showed a rim of enhancement about the periphery of this 1½-cm lesion. Cerebral angiography showed a slight inferior displacement of the anterior inferior cerebellar artery as it passed the plane of the porus acusticus and a slight displacement of the parenchymal branch of the petrosal vein along the anteromedial aspect of the cerebellopontine angle. No tumor blush was noted. The vessel displacement was consistent with the size estimation by CT scan and posterior fossa myelography. Facial nerve threshold electrical excitability tests with the stimulus at the stylomastoid foramen showed the right side to require 2.5 mA more current than the left. Suprathreshold facial nerve stimulation and whole muscle action potential recording at the orbicularis oris showed this myogenic evoked potential to be 1.8% the amplitude of the normal side. Electromyography of the facial musculature showed the right face to be electrically silent at rest. Minimal voluntary contractions resulted in normal motor unit action potentials. Max-

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Presented at the meeting of the American Neurotology Society, Vancouver, British Columbia, May 8, 1981.

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Fig. 1. Serial audiometric results of illustrative case with vascular tumor of the eighth nerve most consistent with cavernous hemangioma. PTA - Pure tone average, decibels, 500-2,000 Hz; PBm - Phonemically balanced word maximum score, percent correct; SSIm - Synthetic sentence identification maximum score, percent correct; STAT - Suprathreshold Adaptation Test; BCL - Bekesy Comfortable Loudness test; Bekesy - Bekesy sweep frequency threshold test; Afferent SR - Stapedius reflex, acoustically induced, afferent limb of the reflex arc, ie, test tone in right ear, probe in left ear and then in right ear; ABR - Auditory brainstem responses; Delay V - Latency delay of wave V; CNE - Could not evaluate; ■ - No response; ▨ - Elevated threshold; ☐ - Normal.

	PTA	PBm	SSIm	STAT	BCL	Bekesy	Afferent S.R.				ABR
							250	500	1000	2000	
8/18/75	33	76%	90%	Neg.	Neg.		■	■	■	■	
8/22/75	35	84%	100%				■	▨	▨	■	Delay V
9/15/75	42	84% Roll-over	100%				▨	▨	■	■	
12/12/75	35	80%	100%	Neg.	Neg.		▨	☐	☐	☐	
10/5/76	38	72% Roll-over	100%	Neg.	Neg.		■	■	▨	▨	
2/21/78	62	0%	0%	Pos.		III	■	■	■	■	
8/16/78	69	CNE	CNE	Pos.							No Response

imal voluntary contractions showed a decreased interference pattern in the right orbicularis oculi and frontalis.

The patient was operated on in December 1978 via a right translabyrinthine approach. The internal auditory meatus was filled with an extremely vascular, firm tumor which extended from the fundus of the canal to 1 cm medial to the porus acusticus within the lateral recess of the pontine cistern. The tumor was tightly adherent to the dura of the internal auditory meatus and at the fundus of the canal anterior to the facial nerve; there the tumor was tightly affixed to eroded bone. The facial nerve was displaced posteriorly about the tumor rather than lying in its usual anterior position; it transversed the posterior margin of the tumor superior-laterally to inferior-medially, spiraling across the periphery of the tumor. It appeared inseparable from the tumor mass for approximately 5 mm just lateral to the porous acusticus. The tumor was totally resected and the ends of the facial nerve were anastomosed. The histopathology of the tumor mass was consistent with cavernous hemangioma (Fig. 2).

RESULTS

The 55 surgically confirmed tumors were composed of 49 solitary schwannomas of the eighth nerve and 6 other neoplasms. The six other neoplasms were: 1 eighth nerve hemangioma, 1 eighth nerve hamartoma, 1 eighth nerve vascular tumor most consistent with cavernous hemangioma, 1 seventh nerve schwannoma, 1 jugular foramen schwannoma and 1 base of skull chondroid cordoma (Fig. 3).

Of the 49 solitary schwannomas of the eighth nerve, 3 had preoperative facial nerve paresis. Of the 6 other neoplasms involving the internal auditory meatus, 4 had preoperative facial nerve paresis. The probability of this distribution occurring by chance was $p = 0.0014$ as measured by the Fisher Exact Probability Test (Fig. 3).

Of three patients with a solitary schwannoma of the eighth nerve and preoperative facial paresis, all lost facial nerve function permanently. In 2 of the 3, the facial nerve was resected as it disappeared within the substance of the tumor; in the other the facial nerve appeared to be anatomically intact following a difficult dissection from the tumor. This patient's facial nerve function never recovered. In the 4 patients with facial nerve paresis resulting from other tumors of the internal auditory meatus, 2 required resection and 2 were anatomically spared and recovered. The 2 that were resected were consumed by the tumor, 1 by a seventh nerve schwannoma and 1 by an eighth nerve vascular tumor most consistent with cavernous hemangioma.

Forty-six of the 49 patients with solitary schwannomas of the eighth nerve had no demonstrable facial nerve paresis preoperatively. Despite this fact, it was necessary to resect the facial nerve in four of these patients when it became intraoperatively apparent that the tumor had invaded the substance of the facial nerve. In the remaining 42 patients, the facial nerve remained intact. Thirty-nine of these 42 patients had satisfactory recovery; 3 of the 42 failed to recover facial nerve function. One of these

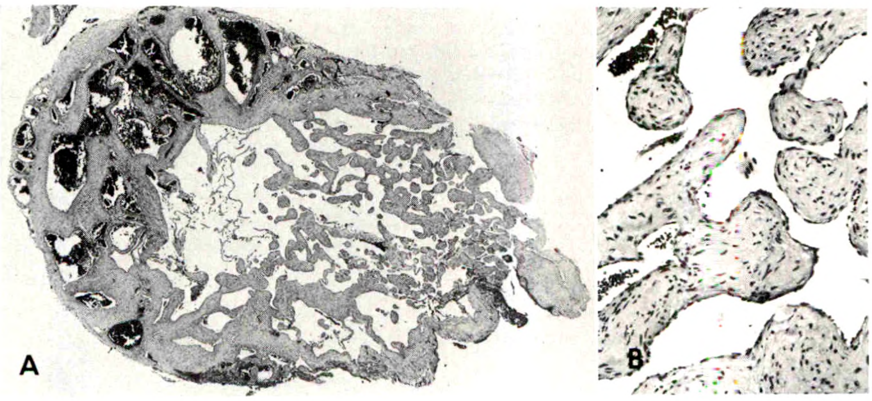

Fig. 2. A) Photomicrograph of a cross section of an en bloc resected eighth nerve-cavernous hemangioma. No eighth nerve fibers could be identified histologically in or around the tumor (H & E, x21). B) Higher power photomicrograph of endothelial-lined vascular spaces seen in A (H & E, x150).

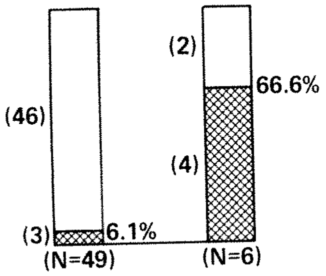

Fig. 3. Distribution of cases of preoperative facial paralysis present in solitary schwannomas of the eighth nerve, and cases of other neoplasms involving the internal auditory meatus.

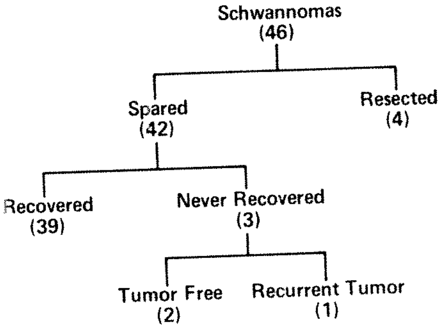

Fig. 4. Postoperative fate of facial nerve function in 46 cases with solitary schwannomas of the eighth nerve and normal preoperative facial nerve function. Numbers in parentheses indicate the numbers of patients involved.

developed a recurrent schwannoma in the vicinity of the facial nerve six years following the initial resection (Fig. 4).

Two of the 6 patients with other neoplasms affecting the internal auditory meatus had normal preoperative facial nerve function. One had an eighth nerve hemangioma and one an eighth nerve hamartoma; in both, the seventh nerve was intact at the end of the procedure and facial function recovered.

DISCUSSION

Brackmann and Bartels,[1] in reviewing 1,354 cerebellopontine angle tumors, found 91.3% were acoustic neurinomas and 8.7% other tumors. Our experiences are similar. Eighty-nine percent of our cases were solitary schwannomas of the eighth nerve, 11% were other neoplasms.

Preoperative facial paralyses resulting from solitary schwannomas of the eighth nerve are unusual. Brow[3] in reviewing 500 patients with these tumors found only 3.2% with facial weakness; slightly more, 5.4%, had facial muscle fasciculations. In our small series 6.1% had facial paresis. In contrast, Portmann et al[4] found facial paralysis much more common "with other swellings involving the internal auditory meatus, such as meningiomas and cholesteatomas." They further emphasized that two observations helpful in differentiating solitary schwannomas from meningiomas are 1) calcification and 2) facial paralysis in meningioma cases. Vascular lesions of the internal auditory canal have a tendency to result in earlier onset of retrocochlear auditory dysfunction and facial weakness.[1,2] Other neoplasms affecting the internal auditory meatus resulting in retrocochlear auditory dysfunction such as astrocytomas, meduloblastomas and metastatic tumors are frequently associated with facial paralysis.[1] In our series, 66.6% of other tumors involving the internal auditory meatus resulted in facial paralysis.

There is some evidence to suggest that facial paresis in cases of solitary schwannomas of the eighth nerve indicate a poor prognosis for facial nerve function postoperatively. One hundred percent of our cases with preoperative facial paresis lost function of their facial nerve. This appears to be the result of gross and microscopic invasion of the facial nerve by neoplastic Schwann cells. This may be true even when there is no preoperative facial paresis. In our series, 15% of the 46 patients with normal preoperative facial nerve function lost the facial nerve ultimately. This is consistent with the findings of House and Leutje[5] who reported 13.5% of 414 patients having total facial paralysis postoperatively.

Tumor recurrence might be expected if tumor invasion of the facial nerve goes unrecognized. In 1 of our 3 cases with normal preoperative facial nerve function but permanent postoperative paralysis of the surgically intact nerve, a recurrent tumor was discovered in the region of the preexisting facial nerve.

In summary, this small number of cases tends to suggest that schwannomas of the eighth nerve, though rarely causing facial paralysis, may infiltrate a normally functioning nerve and, if unrecognized, may interfere with postoperative facial nerve recovery and ultimately result in a recurrent tumor. Tumors other than eighth nerve schwannomas are more likely to result in facial paralysis preoperatively, but seem less prone to infiltrate the normal appearing nerve. Electrical tests of facial nerve function and electromyography did not seem to add prognostic information beyond the clinical observations of facial nerve function.

REFERENCES

1. Brackmann DE, Bartels LJ. Rare tumors of the cerebellopontine angle. Otolaryngol Head Neck Surg 1980; 88: 555-9.

2. Sundaresan N, Eller T, Ciric I. Hemangiomas of the internal auditory canal. Surg Neurol 1976; 6:119-21.

3. Brow RE. Pre- and postoperative management of the acoustic tumor patient. In: House WF, Luetje CM, eds. Acoustic tumors: management. Vol. 2. Baltimore: University Park Press, 1979: 153-73.

4. Portmann M, Sterkers JM, Charachon R, Chouard CH. The internal auditory meatus: anatomy, pathology and surgery. New York: Churchill Livingstone, 1975;193-246.

5. House WF, Luetje CM. Evaluation and preservation of facial function: postoperative results. In: House WF, Luetje CM, eds. Acoustic tumors: management. Vol. 2. Baltimore: University Park Press, 1979:89-96.

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IMMUNE COMPLEXES IN MIDDLE EAR FLUID IN CHRONIC SECRETORY OTITIS MEDIA

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Data on 87 patients (113 ears) with chronic secretory otitis media (SOM) are reported. The bacteriological analysis of the middle ear fluid (MEF) revealed *Streptococcus pneumoniae* in 7% of ears, *Hemophilus influenzae* in 9%, opportunistic bacteria in 20%, while 64% of the samples showed no growth. Free capsular polysaccharide pneumococcal antigens were found in 5% of the MEF samples using counterimmunoelectrophoresis (CIEP) with Omniserum containing 83 different pneumococcal polysaccharide types. Heating of the samples to disrupt the immune complexes increased the frequency of positive samples to 27%. These findings, together with the frequent occurrence of *S pneumoniae* and *H influenzae* in the nasopharynx, strongly support the opinion that chronic SOM in a considerable number of cases is an immune complex disease.

Secretory otitis media (SOM) has been intensively studied during the last 20 years. The bacteriological aspects and the chemical and immunochemical characteristics of the middle ear fluid are well documented as are also the histopathological processes, and immune reactions in the mucosa. It is commonly agreed that infection is a basic etiological factor but it is not clear why the disease is resistant to treatment in a considerable number of children, sometimes resulting in permanent chronic ear disease. This mostly takes the form of adhesive otitis media, as the thick fluid in the ear is subject to organization due to proliferation of fibrous tissue on the mucosal surfaces devoid of epithelium.

Veltri and Sprinkle[1] suggested that the Coombs and Gell type III immune complex mechanism could explain the chronicity of SOM. This reaction necessitates participation of an antigen, an antibody, complement system, and polymorphonuclear leukocytes (PMN). All these are present in the middle ear fluid and the oropharyngeal microbes could well be the source of antigens. The microbes could provide the antigen, also in the absence of an acute suppurative infection at each exacerbation, to react with the locally produced (or transudative) antibody. Following the formation of immune complexes, activation of the complement cascade via the classical or an alternate pathway would occur. PMN and monocytes would be attracted to the middle ear where they would die and release their intracellular contents, particularly lysosomes, into the tympanic cavity, with resultant damage.

Mravec et al[2] tested this hypothesis with an animal model. They injected immune complexes into the middle ear of chinchillas, which were successively killed at intervals after the injection. Intense inflammation was observed in animals killed at 24 hours. The capillary permeability was increased, PMN migrated into the mucosa and both hemorrhage and damage to the subepithelial basement membrane had occurred. These data were consistent with the complement-mediated immune reaction and supported Veltri and Sprinkle's hypothesis of an immune complex disease.

Our study of the mononuclear cells in mucosal biopsies from SOM patients revealed the presence of T-, B-, non-T and non-B lymphocytes, and plasma cells.[3] PMN were generally absent and these cells were only seen passing through the epithelium into the fluid. The changes were similar to those seen in rheumatoid arthritis, and they also lend probability to the idea of an immune complex disease.[3-5]

In this paper we have concentrated upon identifying immune complexes which could have formed with pneumococcal capsular antigens, as pneumococci are the major causative agents in acute otitis media. Antigens can be reliably demonstrated with standardized antisera and their presence in the effusion of chronic SOM would give further support to SOM being an immune complex disease.

PATIENTS AND METHODS

The study was carried out in 87 patients (113 ears), who were admitted to the Department of Otolaryngology for insertion of a middle ear ventilation tube, and adenoidectomy if this had not been made earlier. Middle ear fluid (MEF) was aspirated into a special collector through a myringotomy incision in the anterior quadrant of the tympanic membrane and the sample was stored at -20°C until analyzed. At the same time, samples for bacterial culture and sensitivity testing were taken from 94 ears.

All patients had had definite symptoms of SOM for some time and 39 patients (45%) had been treated in the department several times with ventilation tubes. In 48 of the patients (55%) a ventilation tube was inserted for the first time. The disease was bilateral in 64 (74%) and unilateral in 23 (26%) of the patients.

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TABLE 1. RESULTS OF BACTERIAL CULTURES

Pneumococci	7%
Hemophilus strains	9%
Opportunistic bacteria	20%
No growth	64%
Total aspirates 94	

Bacteriological analysis of specimens from the nasopharynx had been made for part of the 39 patients who came for repeated tube placement, or were taken during the present study.

None of the patients had symptoms of upper respiratory infection at the time of surgery. Nor did any patient have signs of active otitis media, but the middle ear disease was characterized by nearly normal-looking, poorly moving tympanic membrane and thick fluid in the tympanic cavity. There was one single adult patient in the series, having nasopharyngeal carcinoma with total occlusion of the eustachian tube. Ventilation tubes had been kept in this ear for a period of nine years and after extrusion of the tube the fluid had been serous on most occasions.

For counterimmunoelectrophoresis (CIEP) the frozen samples were allowed to thaw in room temperature, and 200 μl of 0.9% NaCl was added to each sample. The sample was carefully mixed in a Vortex mixer (Scientific Industries Inc) and left to stand overnight. CIEP was performed on glass plates coated with 1% agarose gel in barbital acetate buffer (pH 8.2, ionic strength 0.025), the same buffer (ionic strength 0.05) as that used in the buffer reservoirs. Parallel rows of wells with a 4 mm diameter were punched on the plates, 4 mm apart. The wells on the cathodic side were filled with 15 μl of the reactants, and the same amount of Omniserum (Diagnostic Pneumococcal Antiserum, Statens Seruminstitut, Copenhagen) was used in the wells on the anodic side. The electrophoresis was run for one hour at room temperature using a LKB 2121 power supply of 80V with current strengths between 20 and 30 mA. The plates were read for precipitin bands immediately after this, and again after overnight incubation at 4°C.

To liberate the antigen from the immune complexes, possibly present in the MEF samples, the sample was transferred into a small glass tube, 200 μl of 0.9% NaCl was added and the tube heated in a boiling water bath for 5 to 10 minutes. The samples were then allowed to cool, were centrifuged and the supernatant analyzed for pneumococcal antigens with CIEP as described above.

TABLE 2. PRESENCE OF PNEUMOCOCCAL ANTIGENS

Free soluble antigens	5%
Bound in immune-complex	22%
Total aspirates 113	

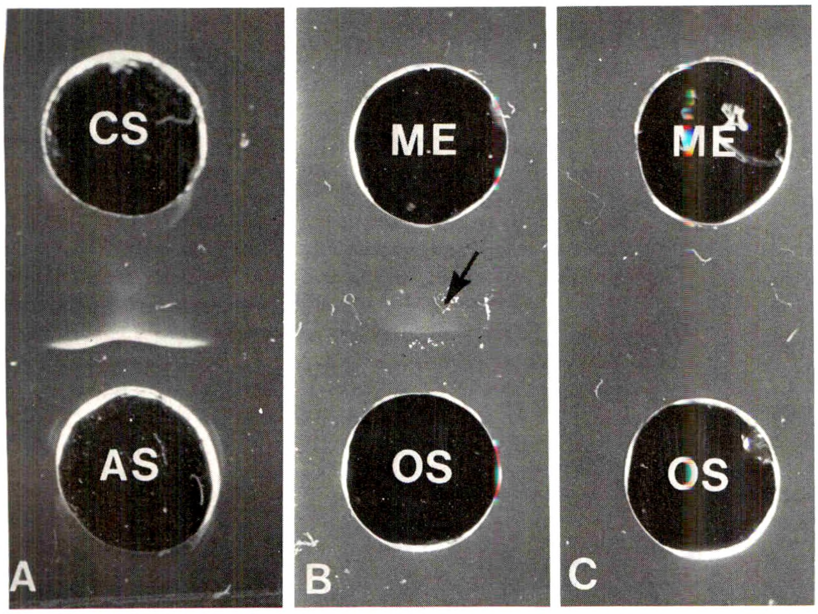
RESULTS

Sixty (64%) of the 94 middle ear aspirates studied revealed no growth of bacteria. *Streptococcus pneumoniae* was found in 7 (7%) and *Hemophilus influenzae* in 8 (9%) aspirates (Table 1). Opportunistic bacteria, mostly staphylococci, were present in 19 (20%) aspirates. CIEP of the 113 aspirates revealed free, soluble pneumococcal antigens in 6 (5%) ears (figure). Heating of the aspirate to disrupt the immune complex produced a clear increase in the number of pneumococcal antigens, 30 aspirates (27%) being now positive (Table 2).

On culture, 3 of the 6 MEF with free pneumococcal antigens were positive for *S pneumoniae*. Pneumococci were also cultured from three of the MEF revealing antigen bound to immune complex but no free antigen. In the bacterial analyses in connection with earlier treatment, pneumococci had been found in 16 of these 64 ears (25%).

MEF samples from the patient with nasopharyngeal carcinoma had on some occasions shown nonpathogenic bacteria but free pneumoccocal antigens or immune complexes were not present.

In the group of 39 patients who had previously been treated with repeated tube insertions, nasopharyngeal swab specimens revealed *S pneumoniae* in 30 patients (80%) and *H influenzae* in 25 patients (64%). During the treatment period which covered several years, both microorganisms had often been present simultaneously and at times either one of the microbes had been identified.



Example of counterimmunoelectrophoretic test run. A) Control run with Anti-Human Albumin Serum (AS), Orion Diagnostica, Finland; and Ortho Normal Control Serum Unassayed (CS), Ortho Diagnostics, Raritan, NJ. Strong precipitin band is seen between wells. B) Positive test run with Omniserum (OS) and middle ear fluid (ME). Arrow points to precipitin band. C) Negative test run.

DISCUSSION

Omniserum is a polyvalent antiserum containing antibodies to 83 different pneumococcal polysaccharide types. Although the less common serotypes 7 and 14 cannot be identified with the buffer used in this study, the antiserum is excellent for screening purposes, and demonstration of pneumococcal antigens in the MEF can be considered diagnostic. Using CIEP and latex agglutination in a study of 472 MEF samples from patients with acute purulent otitis media, Leinonen[6] found that free soluble pneumococcal capsular antigens were present in 88% of the 135 samples from which *S pneumoniae* was cultured. These antigens were also found in 33% of the 202 ears with negative cultures and in 15% of the MEF samples from which other pathogens associated with acute otitis media were isolated. In addition, immune complexes were occasionally detected at the acute stage, the antigen becoming demonstrable after heating of a sample which initially had been negative for pneumococcal antigen.[6]

In acute purulent otitis media 40-50% of MEF samples taken prior to treatment will reveal *S pneumoniae.* In the present cases of chronic SOM with no acute signs at the time of myringotomy and tube insertion, the frequency of positive pneumococcal cultures was typically low (7.4%) and free, soluble pneumococcal, capsular antigens were equally infrequent (5.3%). It was to be expected that the present findings would differ markedly from those made by Leinonen[6] in MEF samples from acute otitis media cases. However, disruption of the immune complex by heating raised the frequency of pneumococcal antigens among all 113 samples of 26.6%. This both bears out the pneumococcal infectious origin of these cases of SOM and lends support to the concept of an immune complex disease put forward by Veltri and Sprinkle[1] as an explanation for the chronicity of SOM.

It is quite probable that in this series the actual number of ears with pneumococcal antigens in the MEF is larger than the 27% demonstrated. This is mainly due to the fact that the CIEP method is clearly less sensitive than, eg, latex agglutination[6] for the common pneumococcal type 19, and to some extent also for type 3. The fact that serotypes 7 and 14 are not detected by CIEP with the used buffer has also affected the results. Thus, it seems likely that *S pneumoniae* antigens were present in the MEF in at least 30% of these SOM cases.

As pointed out by Veltri and Sprinkle,[1] the persistence of the immune complex disease is not dependent on repeated acute middle ear infection, as microorganisms in the nasopharynx could be the most likely source of antigens. The high frequencies of nasopharyngeal cultures positive for *S pneumoniae* and *H influenzae* in the group of truly chronic cases in this study are quite suggestive.

The indication that SOM is an immune complex disease argues in favor of the treatment of acute otitis media which we practice at our department and which we have found to be superior to conservative methods. We advocate early myringotomy and aspiration of the effusion in all ears with purulent acute otitis media to achieve rapid resolution of the infection.[7] If the acute episodes keep recurring we recommend thorough adenoidectomy made under visual control using general intubation anesthesia both to improve the nasopharyngeal airway and to remove tissue that harbors both bacteria and viruses.[8] Adenoidectomy at a later stage when the immune complex disease has already developed is no longer of such importance and help as it is at an early stage of middle ear disease. It could explain why we have achieved good results by performing adenoidectomy early, whereas others on carrying out adenoidectomy at a late stage have found it to be of questionable importance.

REFERENCES

1. Veltri RW, Sprinkle PM. Secretory otitis media. An immune complex disease. Ann Otol Rhinol Laryngol 1976; 85 Suppl 25:135-9.

2. Mravec J, Lewis DM, Lim DJ. Experimental otitis media with effusion: an immune-complex-mediated response. Otolaryngology 1978; 86:258-68.

3. Palva T, Reitamo S, Konttinen YT, Häyry P, Rinne J. Inflammatory cell subpopulations in the middle ear mucosa of ears with effusion. Int J Pediatr Otorhinolaryngol 1981; 3:71-8.

4. Glynn LE. Pathology, pathogenesis and aetiology of rheumatoid arthritis. Ann Rheum Dis 1972; 31:412-20.

5. Kobayashi I, Ziff M. Electron microscopic studies of lymphoid cells in the rheumatoid synovial membrane. Arthritis Rheum 1973; 16:471-86.

6. Leinonen MK. Detection of pneumococcal capsular polysaccharide antigens by latex agglutination, counterimmunoelectrophoresis, and radioimmunoassay in middle ear exudates in acute otitis media. J Clin Microbiol 1980; 11:135-40.

7. Palva T, Holopainen E. Chronic middle ear effusions. In: Jazbi B, ed. Pediatric otorhinolaryngology. Proceedings of the Second International Symposium on Pediatric Otorhinolaryngology, Kansas City, March 8-11, 1978. Amsterdam: Excerpta Medic 1978:163-9.

8. Ruokonen J, Sandelin K. Mäkinen J. Adenoids and otitis media with effusion. Ann Otol Rhinol Laryngol 1979; 88:166-71.

Ann Otol Rhinol Laryngol 92:1983

SUBCLAVIAN VEIN THROMBOSIS SECONDARY TO CHRONIC OTITIS MEDIA

A CASE REPORT

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Complications from otitis media and mastoiditis continue to occur despite modern antibiotic therapy. We report a case of lateral sinus thrombosis and extension to the subclavian vein following a chronic otitis media. This is the first such report of this complication. The presentation and management of lateral sinus thrombosis are also discussed.

In 1881 Bezold and Siebenmann described a neck mass resulting from otitis media in a patient in whom the infection had penetrated the tip of the mastoid medial to the sternomastoid muscle.[1] In the intervening 100 years reports on complications of otitis media focused on otitic and intracranial problems. With the advent of antimicrobial therapy in the 1930s and 1940s such complications became less common.

However, we have recently treated a patient with undiagnosed chronic otitis media who presented with a neck mass and torticollis due to thrombophlebitis of the sigmoid mass and torticollis due to thrombophlebitis of the sigmoid sinus and internal jugular vein. The patient later developed thrombosis of the subclavian vein. This case illustrates an unusual complication of chronic otitis media and we believe this to be the first report of this association.

CASE REPORT

A 30-year-old man was admitted to the City Hospital Center at Elmhurst in April 1981 with a two-day history of tender swelling of the right neck. Three weeks before admission he had noted progressive malaise and fever to 102°C with some pain in the right ear. A diagnosis of acute otitis media had been made at another hospital and a course of oral penicillin and decongestants had been prescribed. Symptoms and signs persisted and the patient was then given antibiotic drops for a presumed otitis externa. Two days before admission he was seen by his internist who noted neck stiffness and pain over the right mastoid region. A lumbar puncture was negative. The patient was then given oral trimethaprim-sulfamethoxisole (Bactrim) and pseudoephedrine (Sudafed).

At the time of admission the patient presented with a firm, well-defined tender swelling at the anterior border of the right sternocleidomastoid muscle along with associated torticollis. The patient denied any history of previous ear infections or vertigo. He had no complaints of headache or dizziness. He was unsure about the duration of his hearing loss, dating it either to the onset of his present illness or possibly to a single episode of foul otorrhea one year previously. The patient complained of dull pain behind the right ear. On examination he had no mastoid erythema or tenderness and the auricle was normally positioned. The external ear canal was patent and nontender. The patient had no nuchal rigidity, photophobia, facial weakness or nystagmus. The tympanic membrane was thickened but showed normal landmarks and mobility.

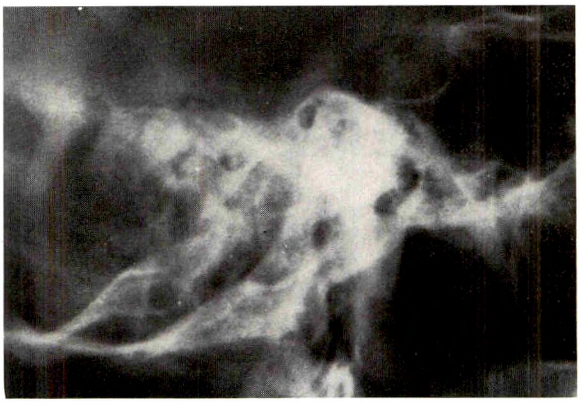

Fig. 1. Lateral view showing cloudy right mastoid with loss of cellular architecture.

An audiogram demonstrated a 50-dB conductive hearing loss on the right side with a discrimination of 92%. Mastoid x-ray films revealed clouding of the right mastoid, loss of cellular separation (Fig. 1), skeletinization of the otic capsule, and the destruction of the tegmen (Fig. 2).

On admission the patient had a temperature of 102°C. His subsequent fevers were noted to have a "picket fence" pattern. The patient had a white blood count of 24,000 with differential: 84 neutrophils, 2 bands, 10 lymphocytes and 4 monocytes. A diagnosis of chronic otitis media and cholesteatoma with extension of infection into the neck was made. Intravenous ampicillin and oxacillin were administered for 36 hours before the patient was taken to the operating room.

The surgical procedure began with exploration of the right neck. Mobilization of the anterior border of the right sternocleidomastoid muscle and entrance into the carotid sheath facilitated drainage of 100 cc of frank pus. The entire right jugular vein was necrotic and thrombosed (Fig. 3). The inferior stump of the vein was traced to the junction with the subclavian vein and was ligated at the base of the neck without significant backflow being encountered. The internal jugular vein was noted to be completely destroyed. No superior portion of the vein could be discerned. A

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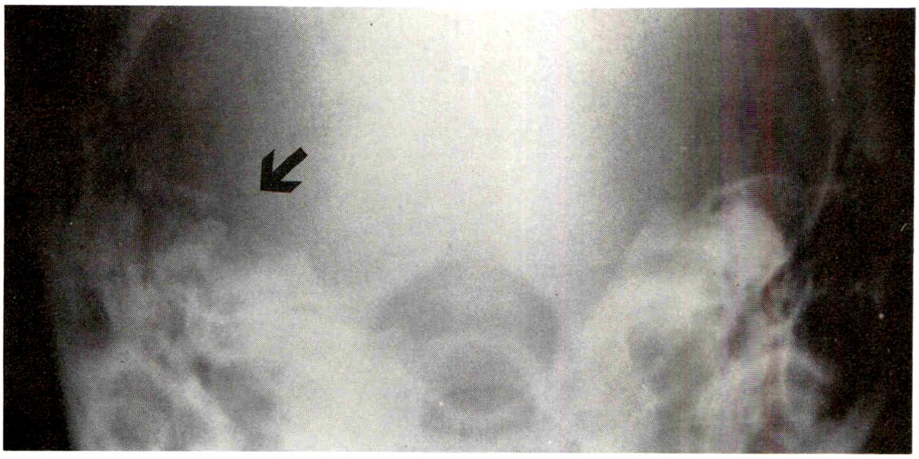

Fig. 2. Towne's view showing right mastoid clouding and destruction of right tegmen (arrow).

Penrose drain was inserted into the neck wound and the wound was closed loosely.

Next, the right ear was prepped and a transcortical mastoidectomy was begun through a postauricular incision. The entire and extensive air-cell system was filled with cholesteatoma. The tympanic membrane was intact. The cholesteatoma extended over the otic capsule which was skeletonized and into the petrous apex requiring retraction of the already exposed dura for removal of the cholesteatoma. The sigmoid sinus was collapsed on itself. Exploration into the sinodural angle demonstrated a perisinus abscess which was drained at this point. There was no infected clot demonstrated within the sinus. A radical mastoidectomy was completed and a large meatoplasty was performed. The incus was noted to be eroded away from the stapes and was removed along with the malleus. The stapes was left in place.

The patient awoke with bilateral chemosis which rapidly resolved. Neurological examination was normal with the exception of the examination of the right ear. The patient was placed into an intensive care unit and given intravenous heparin, chloramphenicol, gentamicin and penicillin, on the advice of the infectious disease consultant. He rapidly became afebrile although his white blood cell count remained elevated for six days. Cultures taken from the pus obtained at surgery initially showed only *Staphylococcus epidermidis*, but later grew anaerobic *Bacteroides* species. On the seventh postoperative day intravenous heparin was replaced by subcutaneous miniheparinization. Two days later the patient developed a fever of 104° C and suffered dramatic swelling of the right arm and tenderness over the right deltopectoral triangle. A venogram confirmed the clinical impression of right subclavian thrombophlebitis (Fig. 4), and the patient was again given intravenous heparin. The previous antibiotics were discontinued and clindamycin was begun. Fever, neck and arm swelling and other clinical signs quickly abated and the patient was discharged on dihydroxycoumadin with no significant sequelae on the 35th day following admission. The mastoidectomy cavity is healing well and there is no evidence of residual or recurrent disease at this time.

DISCUSSION

Complications due to otitis media can be divided into otologic, intracranial and other. Otologic complications include coalescent mastoiditis, petrositis and labyrinthitis while the intracranial group includes extradural, subdural and brain abscesses, lateral sinus thrombosis (LST), meningitis and otitic hydrocephalus.[2] Extension beyond the cranium constitutes an unusual category which includes cervical and distant abscesses and internal jugular vein thrombophlebitis. Thrombosis of the subclavian vein as demonstrated by our patient must be included in this group.

Chronic otitis media may produce a neck mass either from direct extension through the mastoid cortex as described by Bezold and Siebermann,[1] or by producing an internal jugular thrombophlebitis as the present case. Hughes and associates reported a case of an aural cholesteatoma presenting as a large neck mass and noted that only two previous cases were reported in the literature.[3] Their patient had an encapsulated mass of cholesteatoma rather than the frank pus seen in our patient.

Subclavian vein thrombosis resulting from ear infection is most unusual. In a study of 60 patients with thrombosis of the deep veins of the arm (subclavian or axillary) Coon and Willis ascribed none to otologic or cervical causes.[4] In the present case we postulate direct extension from the internal jugular despite ligation as the etiologic mechanism.

In most studies published, meningitis and LST accounted for the majority of complications. However, more recently brain abscesses have been reported in increasingly significant numbers.[5-8] Spread of ear infection to intracranial structures

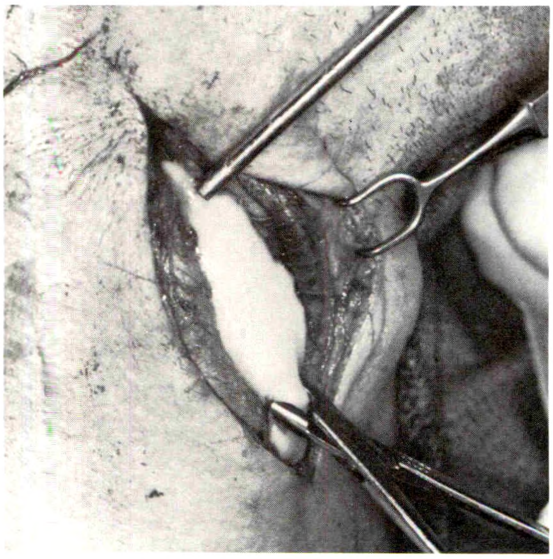

Fig. 3. Surgical drainage of neck abscess deep to sternocleidomastoid muscle.

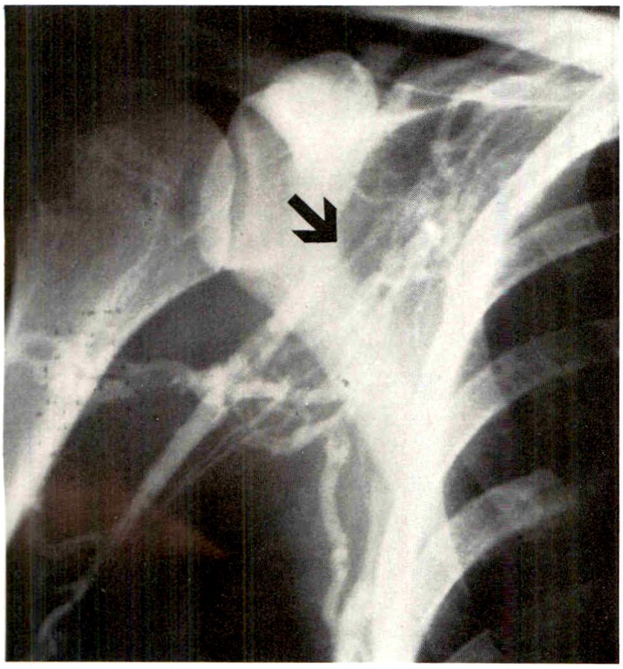

Fig. 4. Venogram revealing occlusion of right subclavian vein (arrow) just medial and inferior to humeral head.

usually occurs along congenitally preformed pathways such as dehiscent sutures, the jugular bulb and venous channels, tegmen, round and oval windows. Other pathways may develop as a result of accidental or surgical trauma. Other mechanisms for spread include bone erosion from cholesteatoma or extension through intact bone by retrograde thrombophlebitis, a phenomenon more frequently associated with acute infections.[2,5]

In discussing the changing patterns of complications of otitis media, Courville reported that from July 1, 1928, through June 30, 1933, approximately 25/1,000 deaths at Los Angeles County Hospital were caused by some complication of otitis media, most commonly meningitis or LST. In contrast, from July 1, 1949, through June 30, 1954, the death rate from these complications fell to 2.5/1 000 and LST was practically eliminated.[7]

In a South African study, Wolfowitz implicated intracranial complications of otitis media in 1/40 deaths in a large general hospital in the five years preceding the introduction of antibiotics. Twenty years later, these complications were fatal in 1/400. In 1972 he reported 28 cases involving 53 complications, including 11 with LST.[9]

Proctor compared the decades 1934-1943 and 1953-1962 and found brain abscesses and meningitis where the most common complaint in both. In the preantibiotic period, 192 complications and 39 deaths were reported while in the antibiotic period only 43 complications and 1 death were noted. The mortality rate specifically associated with LST was 6/16 from 1934-1937 (38%), 7/32 from 1938-1943 (22%). Following antibiotic availability, three cases were reported with only one death. Proctor also noted the frequent association of LST with other complications.[8]

Dawes reviewed 199 complications and found a higher incidence in the younger age groups (10-20 years).[10] Older patients with chronic otitis tended to show multiple complications. LST was noted in 97 patients and 42 of these were associated with other complications. Jensen reported LST as the cause of death in 0.3% of all autopsies performed from 1900-1925, compared to 0.01% from 1956-1960.[11]

Lateral sinus thrombosis typically presents with fever, chills and sweats in a patient with chronic otitis media or acute coalescent mastoiditis. The fever is of the "picket-fence" type in which the patient usually feels and looks well between febrile episodes.[12] There can be associated anemia and hemolysis. Total obstruction is manifested by headache, increased CSF pressure and papilledema. Thrombosis of the mastoid emissary vein produces edema over the mastoid process, Griesinger's sign. Further extension of the infection along dural venous sinuses may result in tender cervical adenopathy, chemosis, proptosis, ophthalmoplegia, retroorbital pain and papilledema. Perivenous edema may produce paresis of the glossopharyngeal, vagal and spinal accessory nerves.[2] Any of the findings could be obscured by an associated meningitis, brain abscess or other intracranial complication.

Evaluation of suspected LST includes complete blood count and blood cultures. A lumbar puncture and CSF examination are helpful not only to ascertain the presence of meningitis or other intracranial infection but also to measure the CSF pressure and to perform a Tobey-Ayer-Queckenstedt test. In this test failure of the CSF pressure to rise following compression of the internal jugular on the involved side, with a normal response on the noninvolved side, suggests LST. Cerebrospinal fluid (CSF) findings are usually negative except for increased CSF pressure.[13]

Surgery is the treatment of choice for LST. Antibiotic coverage should be instituted preoperatively to cover hemolytic streptococci and *Streptococcus pneumoniae* which are the most common organisms.[14] Staphylococci are also seen frequently and Gram-negative and anaerobic Gram-positive organisms are common in patients with chronic otitis media and cholesteatoma. At surgery, the sinus should be evacuated of infected clot and packed off after completion of a simple or radical mastoidectomy.

Although the use of anticoagulants remains controversial, they are indicated when there is evidence of embolization or extension, such as in the present patient who developed subclavian vein thrombosis two days after being switched from intravenous to oral anticoagulants.[15]

Ligation of the internal jugular vein is reserved for cases of continued sepsis or extension of disease.[16] Jahrsdoerfer and Fitz-Hugh discuss the advantages and disadvantages of the procedure and cite such potential complications as circulatory disorders of the brain, retrograde extension of thrombus, injury to the vagus, hypoglossal or spinal accessory nerves and air embolism.[17] Proctor recommends ligation when there is evidence of the clot extending below the mastoid, septicemia or septic emboli.[8] In our patient there was further extension of the thrombus despite ligation.

In summary, this case illustrates an unusual and potentially lethal complication of otitis media which presents with protean symptoms. Just as headache, vomiting and malaise may signal intracranial extension of infection, so do the appearance of a neck mass and torticollis suggest thrombosis of the lateral sinus and internal jugular vein. Propagation of the thrombosis can also involve the subclavian vein as in this patient.

REFERENCES

1. Bezold F, Siebenmann F. Textbook of otology. Chicago: EH Colegrove Co, 1908:182-4.

2. Alford BR, Cohn AM. Complications of suppurative otitis media and mastoiditis. In: Paparella MM, Shumrick DA, eds. Otolaryngology. Vol 2. Philadelphia: WB Saunders, 1980: 1490-509.

3. Hughes GB, Damiani KA, Kinney SE, Levine HL. Aural cholesteatoma presenting as a large neck mass. Otolaryngol Head Neck Surg 1980; 88:34-6.

4. Coon WW, Willis PW. Thrombosis of the deep veins of the arm. Surgery 1968; 64:990-4.

5. Shambaugh GE Jr, Glasscock ME. Surgery of the ear. 3rd ed. Philadelphia: WB Saunders, 1980:289-347.

6. Wright SLW, Grimaldi PM. Otogenic intracranial complications. J Laryngol Otol 1973; 87:1085-96.

7. Courville CB. Symposium on intracranial complications of otitis media and mastoiditis in the antibiotic era. Laryngoscope 1955; 65:31-46.

8. Proctor CA. Intracranial complications of otitic origin. Laryngoscope 1966; 76:288-308.

9. Wolfowitz BL. Otogenic intracranial complications. Arch Otolaryngol 1972; 96:220-2.

10. Dawes JDK. Discussion of intracranial complications of otogenic origin. Proc R Soc Med 1961; 54:315-20.

11. Jensen AM. Sinus thrombosis and otogenic sepsis. Acta Otolaryngol (Stockh) 1962; 55:237-43.

12. Gagnon NB, Sierra-Dupont S, Huot LA, Larochelle D. Thrombosis of the lateral sinus. J Otolaryngol 1977; 6:257-61.

13. Kinal ME, Jaeger RM. Thrombophlebitis of dural venous sinuses following otitis media. J Neurosurg 1960; 17:81-9.

14. Friesner I, Goldman JL, Druss JG, Rosenwasser H. Sinus thrombosis. Am J Surg 1938; 42:116-30.

15. Alford BR, Pratt FE. Intracranial complications from otitis media. Texas Med 1966; 62:66-70.

16. Seid AB, Sellars SL. The management of otogenic lateral sinus disease at Groote Schuur Hospital. Laryngoscope 1973; 83:397-405.

17. Jahrsdoerfer RA, Fitz-Hugh GS. Lateral sinus thrombosis. Southern Med J 1968; 61:1271-5.

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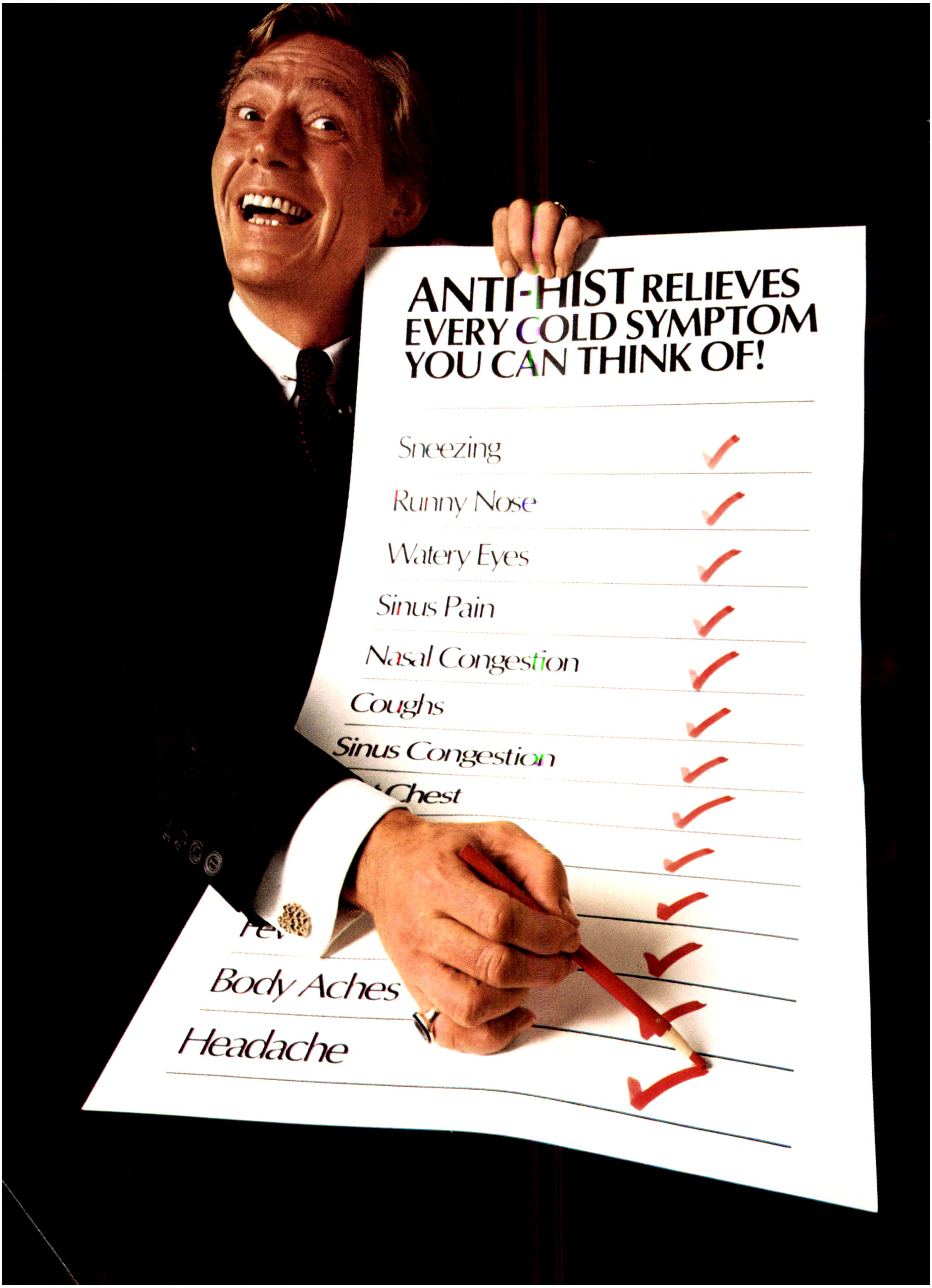
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CONTRAINDICATIONS: ENTEX LA is contraindicated in individuals with known hypersensitivity to sympathomimetics, severe hypertension, or in patients receiving MAO inhibitors.

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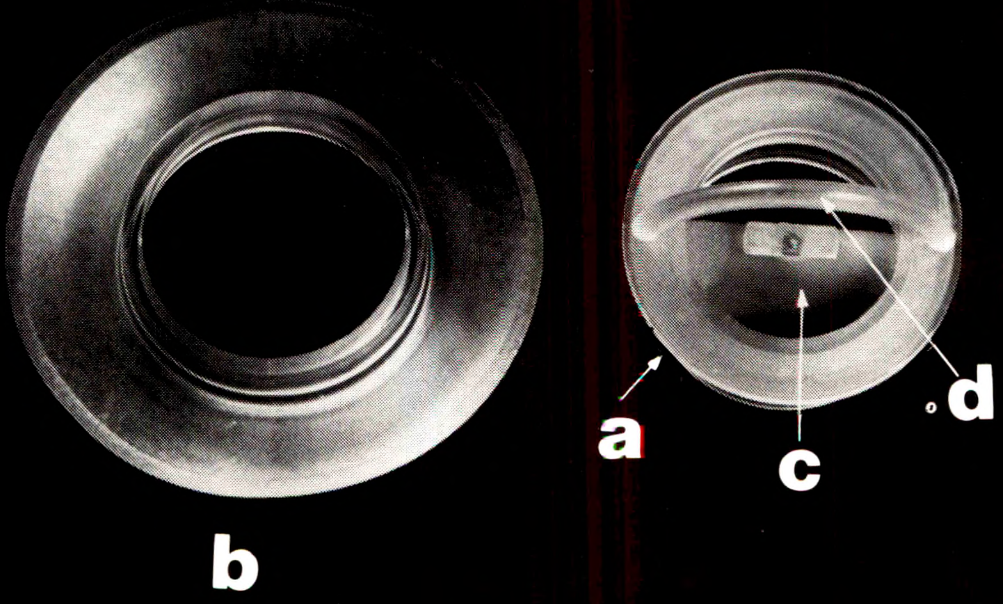

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MALIGNANT TRANSFORMATION OF ADENOLYMPHOMAS

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Adenolymphoma (Warthin's tumor) is a relatively frequent tumor of the parotid gland with characteristic cytological, histological and clinical features. Malignant transformation of the epithelial component of adenolymphomas is extremely rare and not well documented in the literature. In a series of eight adenolymphomas of the parotid gland transition to malignancy was demonstrated cytologically and histologically in one case.

Adenolymphoma (papillary cystadenoma lymphomatosum) or Warthin's tumor is a relatively frequent tumor of the major salivary glands. In 1910, Albrecht and Artz[1] first described this tumor as a morphologic entity and in 1929 Warthin[2] added two cases of his own with an excellent description of their pathology. Since then the name of Warthin has been attached to these tumors.[3]

Adenolymphomas comprise from 5 to 10% of all epithelial neoplasms of the salivary glands.[4] Tumors may arise at any age but develop most commonly in subjects over 40 years of age.[4] Adenolymphomas occur five times as often in males as in females.[5]

The adenolymphoma has been considered an essentially benign tumor. Examples of malignant transformation have been reported infrequently in the past but no case before 1954 could be accepted as proved.[4] In 1960, however, Ruebner and Bramhall[6] described a convincing case of malignancy arising in an adenolymphoma. Even if malignant changes of the oncocytes in adenolymphomas seem to be extremely rare, this possibility should be kept in mind.

METHODS

Of 65 cases of epithelial tumors removed from major salivary glands at Gentofte Hospital between 1976 and 1980, 8 (12.3%) were adenolymphomas. All patients having adenolymphomas were males ranging in age from 51 to 77 years (average 63). The interval between the first symptom, which in all cases was a palpable mass, and the operation ranged from 2 to 54 months (average 20½). In no case was the tumor located in the paraparotid lymph nodes. In one case the tumor was bilateral and in two cases proximal to mixed tumors of the homolateral parotid gland.

Seven of eight adenolymphomas showed a characteristic benign histological picture; in one case a transition to malignancy was demonstrated. This case is described in detail.

CASE REPORT

A 72-year-old male was first seen in July 1979 because of a slowly growing mass in the left parotid gland. He had been aware of the swelling for about a year. Examination revealed a movable tumor measuring 3 x 3 cm. There was no pain and the function of the facial nerve was intact. No enlarged cervical lymph nodes were noted. Aspiration biopsy showed oncocytic cells with marked atypia of the nucleus (Fig. 1). A new aspiration biopsy was performed and this smear showed the presence of lymphocytes, normal oncocytes and only a few with atypia of the nucleus.

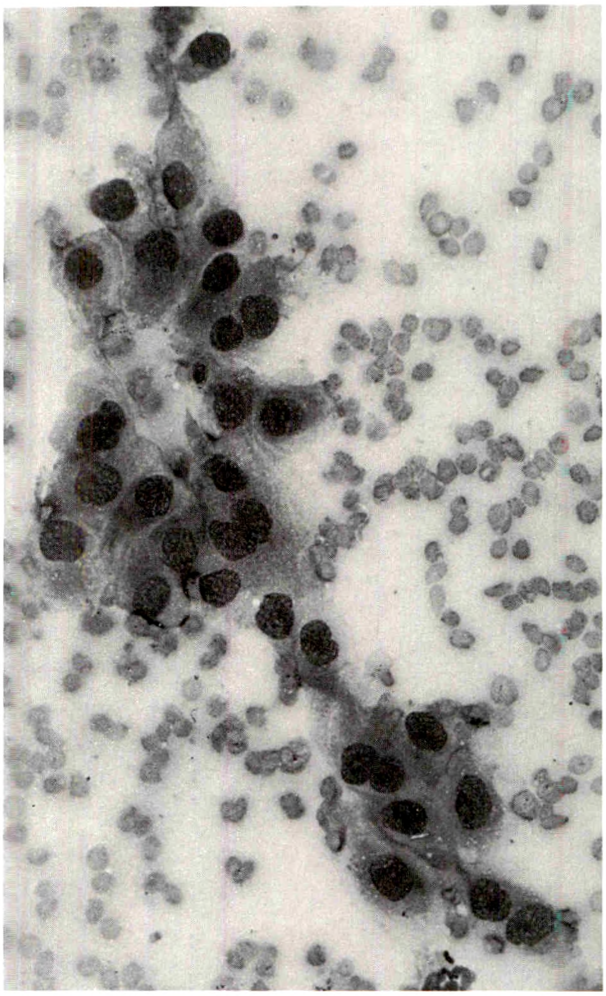

Fig. 1. Oncocytes with finely granulated cytoplasm, sharply demarcated cytoplasm borders and atypical large nucleus with nucleolus. Cells show coherence. (May-Grünwald-Giemsa, x400)

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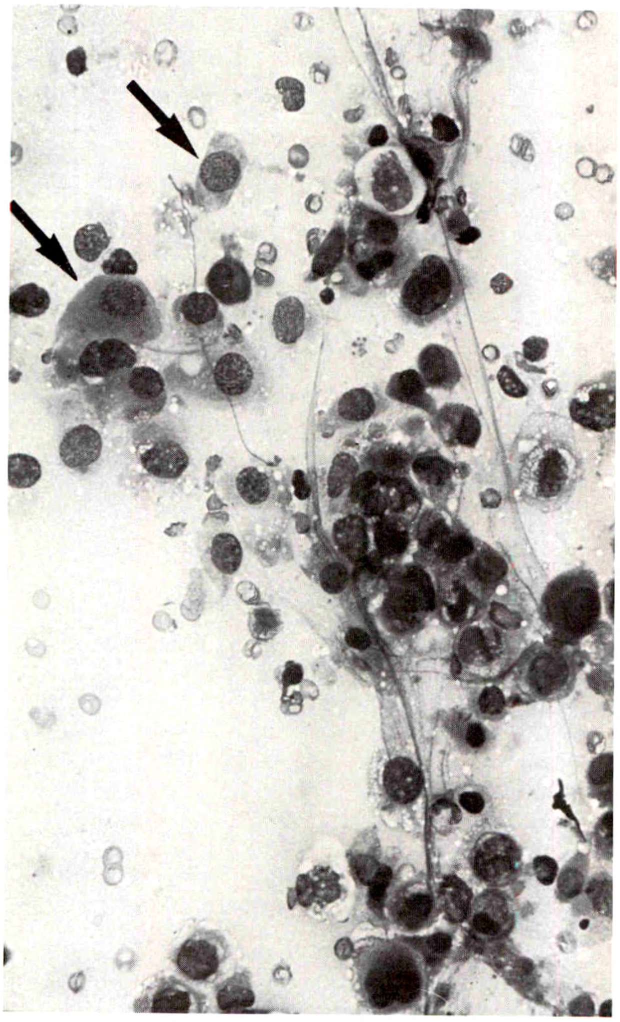

Fig. 2. Epithelial tumor cells and some showing similarity to oncocytes (arrows). (May-Grünwald-Giemsa, x400)

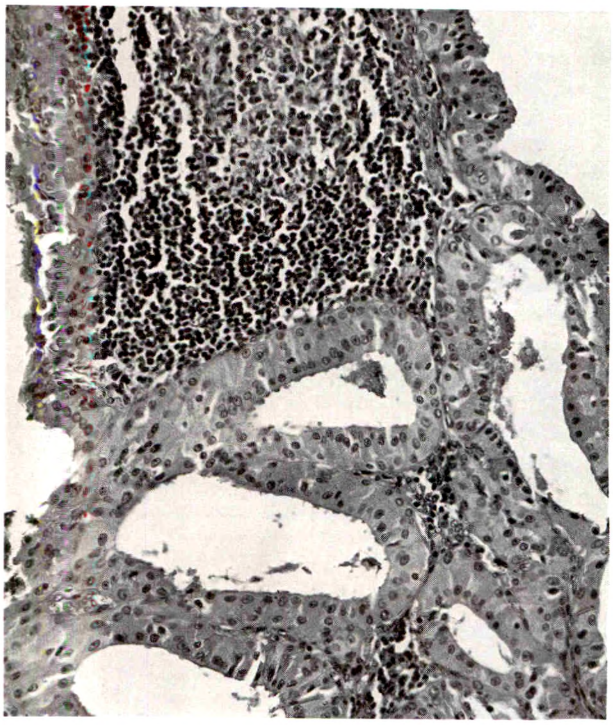

Fig. 3. Typical adenolymphoma with oncocytic epithelium and reactive center in lymphoid stroma. (H & E, x100)

As the lesion seemed to take an uncomplicated, benign clinical course, and the patient preferred to have an operation for a degenerative hip disorder performed first, treatment of the parotid gland tumor was postponed. After the hip operation the patient had severe cardiovascular complications which precluded another immediate operation.

When the patient was examined six months after the initial examination, the parotid tumor had increased in size. Growth had accelerated six weeks prior to the second observation, and although the tumor was still movable it was protruding under the skin. The homolateral submandibular lymph node was enlarged. Aspiration biopsy from the tumor and the lymph node as well showed epithelial tumor cells, some with a clear resemblance to oncocytes (Fig. 2). A parotidectomy combined with a neck dissection revealed the tumor in the parotid. Tumor tissue surrounded the buccal and cervical branches of the facial nerve; there was no infiltration of the skin. Metastases were found in the submandibular lymph node.

The patient died suddenly the first day postoperatively. The autopsy showed an acute subendocardial infarction proved by the Nitro-BT method.[7] No other primary tumor was found and no distant metastases were detected.

Gross and Light Microscopic Findings. The surgical specimen included lymph nodes from the neck dissection, the enlarged submandibular lymph node and the parotid gland measuring 9 x 7 x 5 cm. The gland was nearly totally replaced by nondemarcated tumor tissue. The cut surface was greyish-white and firm with several fine clefts. In the submandibular lymph node the cut surface was greyish-white with necrotic areas. The lymph nodes from the neck dissection were small and appeared normal.

Microscopic examination showed a noncapsulated neoplasm infiltrating salivary gland tissue, vessels, nerves and lymph nodes. In a very small area a remnant of a typical adenolymphoma with well-differentiated epithelium surrounded by lymphatic tissue

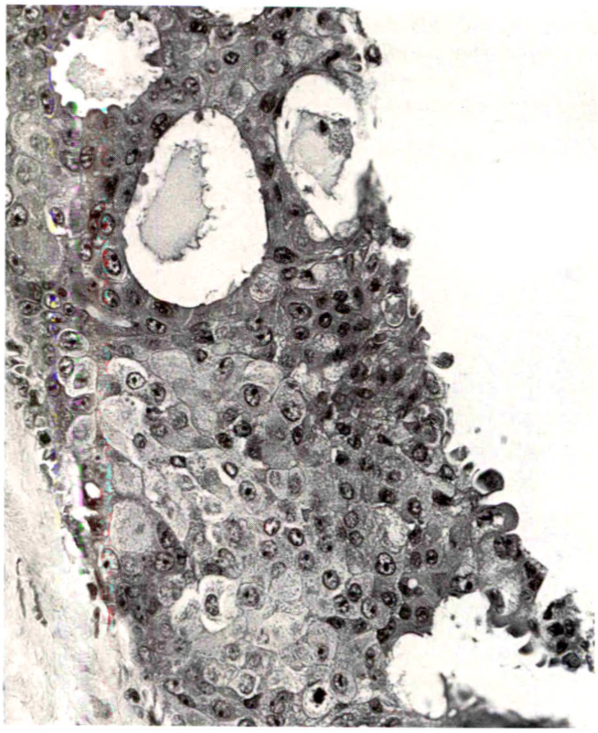

Fig. 4. Cyst lined by a proliferating oncocytic epithelium. (H & E, x250)

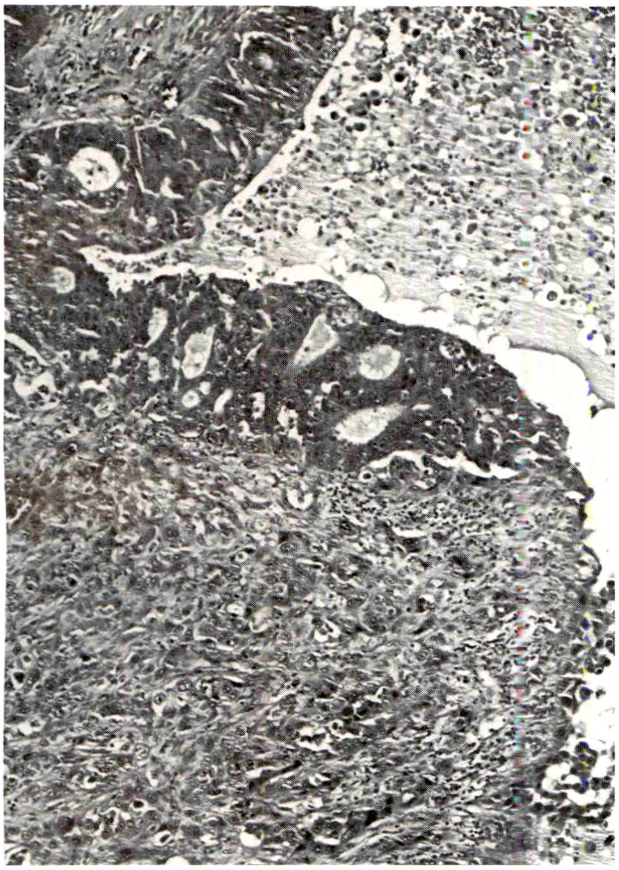

Fig. 5. Fibrovascular connective tissue immediately adjacent to cyst (Fig. 4) is infiltrated by small irregular sheets and acini. (H & E, x100)

was found (Fig. 3). Surrounding this remnant greater cystic spaces containing cellular debris were seen. The cysts were lined by a proliferating papillary epithelium with morphological features characteristic of oncocytes with a distinctly eosinophilic and finely granulated cytoplasm. The nuclei were enlarged and pleomorphic with prominent nucleoli. Mitoses were present (Fig. 4). The carcinoma infiltrating adjacent to the cystic spaces was partly adenomatous with mucus-secreting cells still having an obvious resemblance to oncocytes, and partly poorly differentiated with solid sheets (Fig. 5). The oncocytic character of the tumor cells was confirmed by the phosphotungstic acid hematoxylin (PTAH) stain.[8]

In the submandibular lymph node the carcinoma was adenomatous and trabecular with dedifferentiated oncocytic cells (Fig. 6). No metastases were found in the remaining cervical lymph nodes.

DISCUSSION

Malignant changes of the epithelium of adenolymphomas are extremely rare. In the case presented the tumor of the parotid gland was diagnosed as an adenolymphoma by aspiration biopsy. However, the smear contained oncocytic cells with marked atypia of the nucleus, but due to the usual benign nature of adenolymphomas and a clinical course without pain or facial nerve paresis, no treatment was initiated. In the next half year the lesion seemed to take a benign clinical course, but subsequently clear signs of malignancy appeared with accelerated growth and appearance of a metastasis.

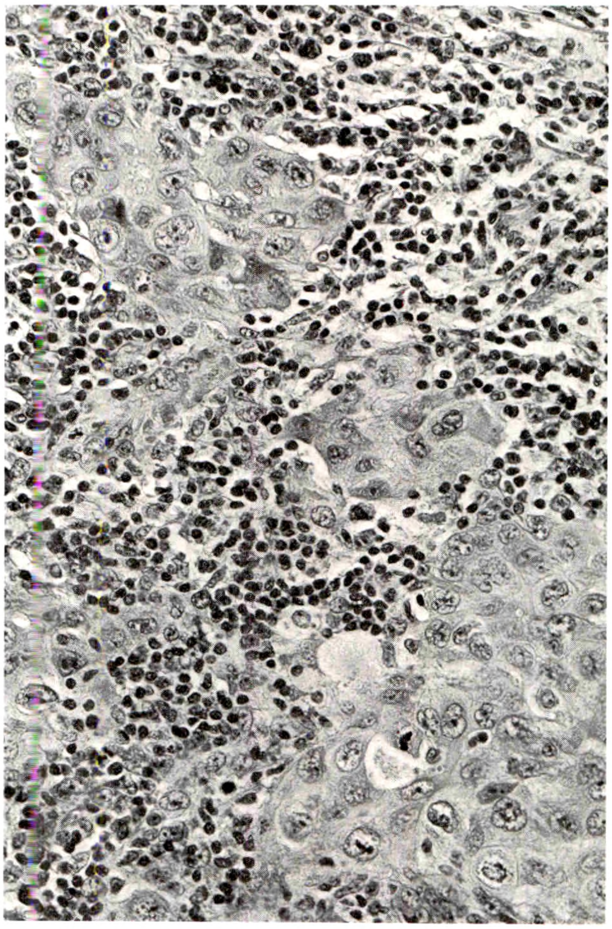

Fig. 6. Solid sheets of tumor cells in submandibular lymph node. (H & E, x250)

All stages from benign adenolymphoma to frank invasive carcinoma, over cysts with progressive epithelial atypia, could be demonstrated both cytologically and histologically. The oncocytic character of the tumor cells could be demonstrated consistently even in the metastasis.

Reports of malignant transformation of the epithelial component of adenolymphomas have been infrequent and generally poorly documented.

Ssobolew[9] described a case of an adenolymphoma with a papillary carcinoma but his illustrations show only coexistence of these tumors.

Cases reported by Nicholson,[10] Stöhr and Risak[11] and Skorpil[12] do not show evidence of malignancy. Hanford[13] reported a patient who developed a squamous cell carcinoma three years after removal of an adenolymphoma but there seemed to be no connection between the two tumors.

Gaston and Tedeschi[14] and Lederman[15] reported cases with metastatic lesions in the cervical lymph nodes, but the primary type and site of the tumors were never proved histologically. The case reported by Lloyd[16] is questionable in that the illustrations approached a morphology more typical of a lymphoepithelioma.

Review of the literature to 1954 thus confirms the opinion of Foote and Frazell[4] that none of these cases of malignant adenolymphomas can be considered proved.

In 1960 Ruebner and Bramhall[6] reported a remarkable case of an adenolymphoma which recurred after eight years and underwent malignant changes but still resembled an adenolymphoma. The description is well documented.

In a case reported by De la Pava et al,[17] squamous metaplasia of an adenolymphoma merging with a squamous carcinoma was observed in a paraparotid lymph node. A neck dissection revealed squamous carcinoma in three separate lymph nodes. The origin of the carcinoma could have been the adenolymphoma, but evaluation and follow-up of the patient for a different primary tumor was desirable.

Little and Rickles[18] described a patient with two proven primary carcinomas, an oat cell carcinoma of the lung and nine years earlier a squamous carcinoma of the larynx. Now an adenocarcinoma infiltrating an adenolymphoma was found. Malignant transformation of the adenolymphoma is a possibility and the illustrations seem to confirm this. The problem is similar in the case reported by Assor[19] where a squamous cell carcinoma of uncertain origin invades an adenolymphoma. The patient had had an adenocarcinoma of the opposite parotid gland 21 months before.

Döbrössy et al[20] presented a patient with an adenolymphoma which recurred and became an anaplastic carcinoma. Gadient and Kalfayan[21] reported a well-documented case of carcinoma that apparently originated from the atypical epithelium of an adenolymphoma located in an intraparotid lymph node. The carcinoma was situated centrally and completely surrounded by the adenolymphoma; no invasion of the capsule was seen.

Moosavi et al[22] reported a case of undifferentiated carcinoma arising from an adenolymphoma. Electron microscopic similarities of the oncocytes of the adenolymphoma and the malignant epithelial cells suggest malignant transformations of the adenolymphoma.

In the literature only sporadic reports of malignant adenolymphomas are found.[6,18,20-22] Some accounts may be of malignant adenolymphomas, but synchronous occurrence of the tumors might be a probable explanation.[17,19]

The adenolymphoma is a histologically and clinically well-defined entity which, for a long time, has been considered completely benign. The very few well-documented cases of true malignancy of adenolymphomas show that malignant transformation is an extremely rare phenomenon but still a possibility not to be overlooked in the diagnostic considerations of tumors of the salivary glands.

REFERENCES

1. Albrecht H, Arzt L. Beiträge zur Frage der Gewebsverirrung: Papilläre Cystadenome in Lymphdrüsen. Frankfurt Z Pathol 1910; 4:47-69.

2. Warthin AS. Papillary cystadenoma lymphomatosum: a rare teratoid of the parotid region. J Cancer Res 1929; 13:116-25.

3. Martin H, Ehrlich HE. Papillary cystadenoma lymphomatosum (Warthin's tumor) of the parotid salivary gland. Surg Gynecol Obstet 1944; 79:611-23.

4. Foote FW, Frazell EL. Tumors of the major salivary glands. Atlas of tumor pathology, Washington, DC: Armed Forces Institute of Pathology, 1954, sec 4, fasc 11.

5. Kleinsasser O, Klein HJ, Steinbach E, Hübner G. Onkocytäre adenomartige Hyperplasien, Adenolymphome und Onkocytome der Speicheldrüsen. Arch Klin Exp Ohren Nasen Kehlkopfheilkd 1966; 186:317-36.

6. Ruebner B, Bramhall JL. Malignant papillary cystadenoma lymphomatosum: report of a case, with brief review of the literature. Arch Pathol 1960; 69:118-25.

7. Andersen JA, Hansen BF. The value of the Nitro-BT method in fresh myocardial infarction. Am Heart J 1973; 85:611-9.

8. Sanford RI, Olen E, Hansen LS. The eosinophilic cells of the parathyroid (oxyphil cells), salivary (oncocytes) and thyroid (Hürthle cells) glands: light and electron microscopic observations. Lab Invest 1962; 11:933-41.

9. Ssobolew LW. Zur Kasuistik der Branchiome. Frankfurt Z Pathol 1912; 11:462-5.

10. Nicholson GW. Studies on tumour formation. Guy's Hosp Rep 1923; 73:37-64.

11. Stöhr F, Risak E. Klinik und Anatomie der Parotisgeschwülste Arch Klin Chir 1926; 143:609-48.

12. Skorpil F. Zur Histologie und Histogenese des papillaren Cystadenolymphomas der Parotisdrüse. Frankfurt Z Pathol 1939-1940; 54:181-9.

13. Hanford JM. Branchiogenic adenoma of the neck. Ann Surg 1931; 94:461-4.

14. Gaston EA, Tedeschi CG. Adenolymphoma of the parotid and submaxillary salivary glands. Ann Surg 1946; 123:1075-89.

15. Lederman M. Adenolymphoma of the parotid salivary gland. Br J Radiol 1943; 16:383-5.

16. Lloyd OC. Salivary adenoma and adenolymphoma. J Pathol Bacteriol 1946; 58:699-710.

17. De la Pava S, Knutson GH, Mukhtar F, Pickren JW. Squamous cell carcinoma arising in Warthin's tumor of the parotid gland. Cancer 1965; 18:790-4.

18. Little JW, Rickles NH. Malignant papillary cystadenoma lymphomatosum: report of a case, with a review of the literature. Cancer 1965; 18:851-6.

19. Assor D. Bilateral carcinoma of the parotid, one cancer arising in a Warthin's tumor. Am J Clin Pathol 1974; 61:270-4.

20. Döbrössy L. Rónay P, Molnár L. Malignant papillary cystadenoma lymphomatosum. Oncology 1972; 26:457-65.

21. Gadient SE, Kalfayan B. Mucoepidermoid carcinoma arising within a Warthin's tumor. Oral Surg 1975; 40:391-8.

22. Moosavi H, Ryan CK, Schwartz S, Donnelly JA. Malignant adenolymphoma. Hum Pathol 1980; 11:80-3.

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COCHLEAR IMPLANT EFFECTS ON THE SPIRAL GANGLION

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To evaluate the effects of chronic intrascalar implants on spiral ganglion cells, we studied 15 monkey cochleas that had had implants for periods ranging from 1 to 28 months. All cases exhibited loss or ongoing degeneration of cells. Cell loss typically was greater in the basal turn, where the implants were located, than at more apical locations. Increasing apical damage was a function of postimplant survival time. Preimplant local treatment of the inner ear with neomycin did not influence the loss of spiral ganglion cells. Osteoneogenesis occurred in the majority of cases, appearing in the basal turn with occasional extension into middle and apical turns. Cell loss was inconsistently associated with new bone formation. Electrical stimulation had no obvious influence on cell survival.

Scala tympani implants are being used with increasing frequency for the amelioration of total deafness, although they provide relatively limited acoustic rehabilitation.[1] Placing electrodes in the scala tympani to improve hearing may create tissue changes that limit or reduce long-term usefulness. Trauma caused by implantation or stimulation may accentuate existing cochlear pathology.[2,3] However, information on such effects in the human cochlea is minimal. One clinical case with bilateral implants has been available for thorough histologic study.[4] In this instance, the individual had scala tympani free-wire implants for several years preceding death. Both cochleas were filled with bone, and there was extensive destruction of cells in the spiral ganglion and eighth nerve axons.

A major difficulty in interpreting such clinical materials stems from our inability to disentangle preimplant pathology from "spontaneous" degeneration of the system subsequent to (and perhaps independent of) receipt of an implant, and from specific effects related to the implant. It is unlikely that these issues can be resolved through information derived solely from clinical material. We have no means for evaluating detailed pathology of the cochlea in a patient at the time of implantation. Moreover, most of these cases are complex, with diverse pathologies underlying the deafness.

The various etiologies of deafness yield a spectrum of sensorineural pathologies which may be compounded at implant surgery. It has been noted that cochlear trauma of various types can lead to widespread ganglion cell degeneration.[5,6] Local infection may also produce general losses, including destruction of spiral ganglion cells,[7] but such outcomes are not always seen in response to insult.[8] Ototoxic drugs destroy organ of Corti structures,[9] under some conditions without corresponding destruction of ganglion cells.[2,5] In all of the types of cochlear trauma, there is insufficient information from which to predict the course of pathology associated with a cochlear implant.

Studies using experimental animals have revealed a number of pathological changes associated with scala tympani implants. In cats, implants can induce formation of a surrounding fibrous capsule, degeneration of the organ of Corti, and osteogenesis in the scalae.[10-14] In monkeys we observed that scala tympani implants provoke encapsulation, loss of organ of Corti structure and loss of myelinated fibers in the osseous spiral lamina. We have also found evidence for degeneration of cells in the spiral ganglion. A comparison between a molded electrode designed to fill the scala tympani of the basal turn and a small diameter electrode that fits loosely in the scala tympani revealed that the former yielded greater damage, but both created pathological changes in the cochlea.[15]

In the present report we describe quantitatively our observations concerning the effects of free-fit, multielectrode scala tympani implants on the survival of spiral ganglion cells.

METHODS

We studied 15 implanted ears and 3 normal unimplanted control ears, all from young adult monkeys (1 *Macaca nemestrina*, 14 *M mulatta*, 2 *M fasicularis*, 1 *M arctoides*). In several cases the animals were behaviorally tested to verify that hearing was normal. All were examined otologically at surgery and exhibited no evidence of outer or middle ear pathology. In aseptic surgery we implanted the anesthetized animals with a slender, free-fit silicon rubber carrier with four platinum-iridium wires (25 μm diameter) that served as stimulating electrodes. The electrodes terminated in uninsulated balls (200 μm) distributed along one surface of the carrier.[16] Following a postauricular approach to expose the round window, we inserted the implant 8-12 mm into the scala tympani. In three cochleas (154R, 153R, 251R) we infused neomycin sulfate (10% w/v) directly into the round window just before inserting the scala tympani implant.

Survival after the implant surgery ranged from 1 to 28 months. During this interval six monkeys (316L, 264L, 350R, 153L, 153R, 251L) received regularly scheduled stimulation through elec-

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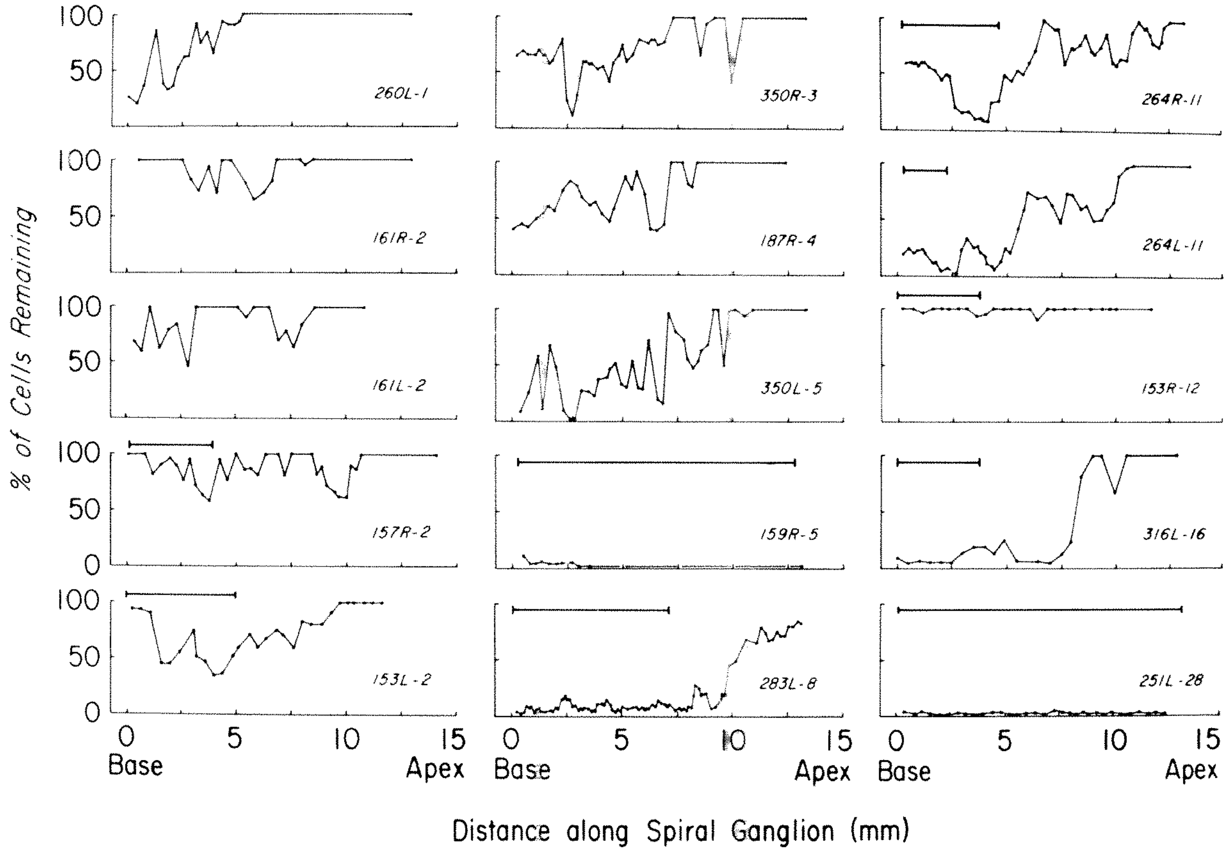

Fig. 1. Individual summary graphs showing percentage of cells remaining in spiral ganglion of monkeys with scala tympani implants. Graphs are based on counts of cells in every 10th or every 5th paramodiolar section. In each graph the animal identification number is followed by a number indicating the months of survival after receipt of implant. A bar above some of the cell profiles identifies presence and extent of osteogenesis in the cochlea. Note that animals 159R-5, 153R, L, and 251L received intracochlear neomycin at the time of implant surgery.

trodes in the implant while they performed psychophysical tasks. Stimuli were charge-balanced, biphasic square or sine waves, 1-1000 μA, 16 Hz-32 kHz. (See Pfingst et al[16] for further details.) Other animals underwent irregular and infrequent stimulation for studies of brainstem evoked response. One animal (161R) received no electrical stimulation during the implant period.

Upon completion of behavioral studies, or a predetermined elapsed survival period, the animals were given a lethal dose of pentobarbital. The middle ear was exposed and flooded with neutral buffered formalin, then immediately perfused with saline and then buffered formalin. The cochlea was removed, the implant was extracted, and the cochlea was stored in buffered formalin for 2-3 weeks. After decalcification the tissue was embedded in celloidin and cut in a paramodiolar plane at 22 μm. Every tenth (in some instances, every fifth) section was stained with hematoxylin and eosin (H & E). In selected cases, adjacent sections were stained with Holmes' silver or Luxol fast blue.

All cochleas were oriented in a similar plane for sectioning. The cells of the spiral ganglion were counted in all of the H & E sections, using an ocular grid at 400x. Each identifiable ganglion cell was counted as "surviving" regardless of its apparent condition. This provided a conservative estimate of neural loss and damage. The counts were plotted as summary representations of the spiral ganglion from base to apex, using a modification of Guild's[17] procedure. In experimental animals, the number of cells in each section was plotted as a percentage of the average number in the equivalent region based on observations from the three normal specimens.

The length of the spiral ganglion was estimated by measuring along the inner margin of the scala tympani, starting 2 mm from the round window. This overestimates the length that would be derived from taking the centroid of Rosenthal's canal. The differential was not deemed crucial to establishing the population of the spiral ganglion.

RESULTS

The estimated population of cells in the spiral ganglion of the three unimplanted monkeys was 45,540, 35,670, and 48,240 (average: 43,150). They were distributed along a length of 12.5-13.6 mm, forming a spiral of two turns. Because the second turn segment of the spiral ganglion merges into a terminal bulb (containing cells serving the third turn and helicotrema region of the basilar membrane), the length of the spiral ganglion is difficult to specify accurately. Cell packing density is greatest in the second turn of the spiral ganglion (12.5 cells/10^{-5}cm^3). The segment of the spiral ganglion representing the hook region is characterized by a packing density that is approximately half the second turn value.

All implanted animals exhibited spiral ganglion cell loss in the segment corresponding to the basal turn of the cochlea, even those whose implants had been in place for just one month and the animal whose implanted ear was not stimulated. Figure 1 shows the extent and distribution of surviving cells

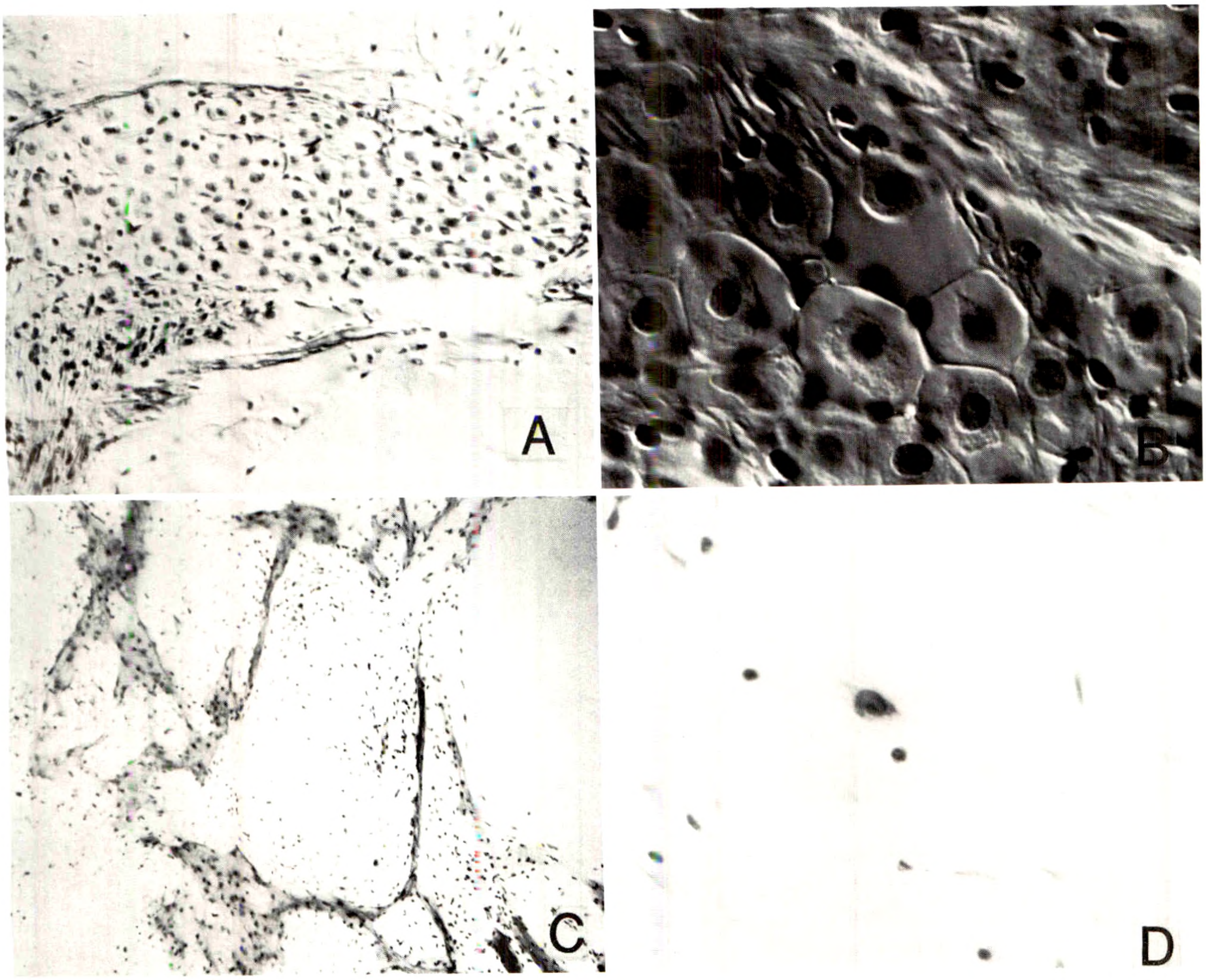

Fig. 2. Reaction of spiral ganglion cells in basal turn to chronic intrascalar implantation at two survival periods: A,B) 3 months (161L); and C,D) 28 months (251L). A - x160, B - x400, C - x160, D - x400)

in the spiral ganglion of each animal receiving an implant.

The magnitude of cell loss from the spiral ganglion varied considerably, even among animals of roughly comparable implant periods. Monkeys with shorter implant periods (less than four months) had a higher percentage of surviving cells than did those with longer implant periods.

Certain characteristics were common to all of the specimens. There were degenerating cells that exhibited chromatolysis, pyknosis, and loss of peripheral dendrites. Such cells were found intermingled with apparently normal cells, although surviving cells were found somewhat more frequently in sites furthest from the osseous spiral lamina.

Figure 2 illustrates the occurrence of early degenerative changes (3 months) following implantation, as well as the continuation of cell degeneration over the longest survival period (28 months). This figure portrays sections from similar regions of the spiral ganglion. At three months (Fig. 2A,B), the distribution and density of cells were almost normal, although occasional degenerating cells appear. At 28 months postimplant there were few cells remaining in Rosenthal's canal (Fig. 2C,D), and approximately one third of those remaining seemed to be degenerating.

The animals implanted for periods of four months or less had relatively limited spiral ganglion cell degeneration beyond the basal region and, for the most part, exhibited 50% or more surviving cells in the basal segment. Few degenerating cells were found in the region representing middle and apical turns of the cochlea. The more prolonged implant periods revealed greater loss locally at the level of the implant and to a lesser extent, apical to this region. In all six cases of eight months or longer implant time, degeneration of at least some of the cells in the apical region was noted, but a clear reduction in the percent of surviving cells did not always appear (Fig. 1). Of these long-term survivors, three had a much larger percentage of normal-appearing cells in the apical region than in the basal turn. Two ears (159R, 251R) exhibited pervasive intrascalar osteogenesis and had few cells at any point of the spiral ganglion. One of these (159R) had a survival time of only five months. Both of these ears had undergone intrascalar perfusion of neomycin at the time of implant. The cochlea of 153R (which also was infused with neomycin) exhibited virtually no loss of cells from the spiral ganglion. Two ears (264R, 264L) that had the same implant time as 153R, but were not treated with neomycin, showed a loss of spiral ganglion cells in the basal turn.

In summary, only one animal with a prolonged implant (153R) exhibited good preservation of spiral ganglion cells, and this animal demonstrated degeneration in perhaps 10-15% of the cells.

In one instance (264R-11), we were able to locate accurately the closely spaced tips of the individual electrode wires embedded in the silicon-rubber implant, inasmuch as the fibrous capsule formed about the implant remained in situ after removal of the implant. Slight cupping occurred at points in the fibrous capsule corresponding to the electrode termination sites. The number of myelinated fibers was reduced in osseous spiral lamina in this sector. Less than 30% of ganglion cells survived in the section adjacent to the electrodes (2.5-5 mm segment), while nearly 60% survived in regions both basal and apical to electrode placement (Fig. 1).

Monkey 161 had bilateral implants introduced concurrently; the right ear received no active stimulation, while the left ear underwent frequent electrical stimulation at a normal operating level. The spiral ganglion on the unstimulated side exhibited definite, albeit limited, degeneration at two months postimplant. In particular, the number of cells in the basal segment was 50-70% of normal. There was perhaps slightly greater loss of spiral ganglion cells on the stimulated side (Fig. 1, 161L-2), an effect seen mainly in the basal turn. In this one case permitting a stimulated/nonstimulated comparison, there was no striking contrast in cell survival patterns between the two sides. Thus, two months of electrical stimulation at the levels used here could not be identified as a significant determinant of cell survival. Further evidence of an indirect nature that bears on this question was obtained through comparisons with other cases. Thus, losses equaling or exceeding those exhibited in the basal spiral ganglion region of either 161L or 161R were observed in an animal that received stimulation for a one-month period (Fig. 1, 260L-1). Two other animals that underwent stimulation over a two-month survival period (157R-2; 153L-2) gave evidence of slight-to-moderate loss that extended beyond the basal region to include cells almost as far as the apex of the spiral ganglion. None had damage of basilar membrane or osseous spiral lamina.

Osteoneogenesis was found in association with the implants in all animals that had survival periods of four months or longer. The cochleas exhibited formation of lamellar bone in one or more scalae, as indicated in Figure 1 by the horizontal bar above the distribution profiles. Bone growth was observed after only two-months' survival in two cases (157R-2, 153L-2). In most new bone, growth was confined to the hook region or to the basal cochlear turn, extending in patches along the length of the implant. However, evidence for more general development of bone beyond the apical termination of the implant was observed in some cases (283L-8, 159R-5, 251L-28). Two of these received intracochlear neomycin at the time of implantation. They had patches of new bone throughout the cochlea, extending into all scalae. In all the cases, the density of the bone was greater with extended survival periods.

DISCUSSION

This work demonstrates that free-fit scala tympani implants typically produce degenerative changes in the spiral ganglion cells. The implants frequently have progressive, destructive effects on inner ear elements that may continue over prolonged periods. Deterioration in the population of spiral ganglion cells begins early in the postimplant period and continues for an indefinite time. The process appears to be selective since not all cells concurrently exhibited pathological characteristics. Both healthy and degenerating cells were found in all animals, although few of the former were seen at 28 months postimplant.

The spiral ganglion changes occur first in cells serving the region that contains the implant. Evidence of cell loss was found within one month after an implant was made. The effect appeared to be restricted to the basal region in the early weeks after implantation. Extension of degeneration to include somewhat more apical regions began within four or five months. This extension cannot be accounted for on the basis of mechanical trauma involving dendritic terminals, since no direct contact with the implant was possible at these levels. Acute trauma at the time of implantation may be responsible for part of the degeneration effects seen in the animals we studied. However, the evidence of continuing degeneration as late as 28 months suggests that other factors operate to promote or sustain the morbidity.

We cannot, of course, specify the condition that may evolve with a very prolonged survival period. Inasmuch as active degeneration was noted at 28 months, a "final" state may not occur for a very prolonged time after implantation. It is a matter for conjecture whether virtually all cells of the spiral ganglion might disappear subsequent to a scala tympani implant. The observations made by Johnsson et al[4] are consistent with this possibility, although preimplant loss may have been an indeterminate contributor in that case. At autopsy there were very few spiral ganglion cells. Schindler and Merzenich's study[18] found a large percentage of surviving ganglion cells following chronic scala tympani implantation in the cat. Behavioral studies of implanted monkeys indicate that absolute sensitivity to intracochlear stimulation remains relatively unchanged over long periods;[16] this has also been reported, somewhat anecdotally, in humans.[1] From such evidence we infer that at least some of the spiral ganglion cells must remain functional for extended periods. However, behavioral observations also demonstrate a correlation between threshold sensitivity, dynamic range of hearing and histopathological state of the cochlea.[16] Obviously a continuing process of degeneration that stabilizes with only a few excitable inner ear elements would result in a system that is capable of only limited resolution of complex input. This becomes a major consideration with a multichannel implant.

The possibility that electrical stimulation may have deleterious effects on the spiral ganglion cells requires further attention. We did not systematically manipulate the parameters of stimulation in this study. We noted one case (264R-11) that had localized cell loss in a region adjacent to electrodes that were actively stimulated. None of the other animals had an identifiable similar pattern, but this may reflect our inability to locate the precise position of electrodes in the basal turn. Perhaps stimulation is not ordinarily injurious to nerve fibers or spiral ganglion cells. The bilaterally implanted monkey that had no stimulation in one cochlea indicated little or no differential damage associated with the electrical stimulation. Certainly, stimulation at moderate and high current values can produce cochlear pathology,[19,20] but intermittent low-level current may have little effect.[21] We believe there are insufficient observations of chronic implants to determine whether the normal operating levels of stimulation used to elicit auditory perceptions on a routine basis contribute to inner ear damage.

One may question whether the cell losses we have observed associated with the implant rule out its practical long-term use. Two considerations may be raised in regard to this question. First, substantial losses of spiral ganglion cells may not constitute a deterrent to the use of scala tympani implants for many prosthetic purposes. Despite the concern expressed by Otte et al[2] regarding the minimum number of cells necessary for speech perception (and, by inference, for screening implant candidates), more modest functional outcomes may be acceptable. Perhaps a few channels of information could be maintained in the presence of severe spiral ganglion cell loss. This could occur if a few cells survive with appropriate separation to permit selective activation. These channels could continue to provide important discriminative information if properly identified and stimulated. Until the full course of degeneration is known (including magnitude of effect and time course of the process), it will be difficult to forecast the potential information-carrying capacity of a scala tympani electrode. It is already known that the individual can perform useful discriminations with few surviving cells.[4,16] The second consideration arises from our findings in one subject (153R) which stands out as a long-term implant, with neomycin pretreatment, extensive new bone growth and yet little spiral ganglion cell loss. We cannot identify experimental factors that account for this somewhat inconsistent finding. Perhaps, however, for developmental purposes we may focus on our "best" observations, but for clinical purposes in this field we must focus on our "worst" findings.

The occurrence of osteoneogenesis in a substantial number of our animals, and the evidence that this effect may be associated with relatively greater ganglion cell loss, indicates a need for attention to 1) factors governing bone formation, and 2) influences of intrascalar bone growth on spiral ganglion cell survival. The initial formation of new bone within the scalae may be a result of trauma or infection at the time of implantation. Fractures of the cochlea wall or damage to the endosteal tissue can contribute to intrascalar osteoneogenesis.[2,12,14,21,22] There is insufficient information to determine the extent to which events of this type occurring at the time of implantation may explain our results in the monkey. These seem unlikely explanations for all ears with new bone growth. In some of our material with restricted new bone, very careful examination of soft tissues in the vicinity of the osteogenic foci revealed little evidence of mechanical trauma. Extensive mechanical trauma might be assumed in the case of one animal (283L-8) that extracted its implant two months following initial surgery (the implant was immediately replaced and retained for an additional six months). This animal exhibited bone growth in basal and middle cochlear turns, but at the time of sacrifice, the apical region was clear. Perhaps with longer survival time the osteogenic process may have continued until all scalae were filled. None of the other monkeys had histories of similar trauma. The animals we studied were not kept under study for a sufficiently long time period to determine whether there may be an obligatory, progressive development of intrascalar bone independent of the routine stimulation protocols that were employed during their behavioral testing. Scalae infiltration was incomplete at 16 months postimplant (316L) but at 28 months we observed new bone in all turns (251L).

Treatment with neomycin at the time of implant placement may potentiate factors leading to new bone growth in the cochlea, but this need not necessarily result in degeneration of cells of the spiral ganglion. Direct effects of neomycin on these cells seems remote, given the extensive information on ototoxicity.[5] All three animals we subjected to intrascalar neomycin had new bone formation, but one of them had very little apparent cell loss after 12 months. At comparable survival periods other ears (without neomycin) had limited osteogenesis accompanied by variable degree of cell loss. It seems likely that multiple factors enter into the control of spiral ganglion cell survival following intracochlear implants.

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REFERENCES

1. House WF. Cochlear implants. Ann Otol Rhinol Laryngol 1975; 85 Suppl 27:1-93.

2. Otte J, Schuknecht HF, Kerr AG. Ganglion cell populations in normal and pathological human cochleae. Implications for cochlear implantation. Laryngoscope 1978; 88:1231-46.

3. Hambrecht FT. Current status of multichannel cochlear prostheses. Ann Otol Rhinol Laryngol 1978; 88:729-33.

4. Johnsson L-G, House WF, Linthicum FJ. Bilateral cochlear implants: histological findings in a pair of temporal bones. Laryngoscope 1979; 89:759-62.

5. Kerr A, Schuknecht HF. The spiral ganglion in profound deafness. Acta Otolaryngol (Stockh) 1968; 65:581-98.

6. Johnsson L-G. Sequence of degeneration of Corti's organ and its first-order neurons. Ann Otol Rhinol Laryngol 1975; 83: 294-303.

7. Sando I, Harada T, Loehr A, Sobel JH. Sudden deafness. Histopathologic correlation in temporal bone. Ann Otol Rhinol Laryngol 1977; 86:269-79.

8. Lindsay JR. Profound childhood deafness inner ear pathology. Ann Otol Rhinol Laryngol 1973; 82 Suppl 5.

9. Leake-Jones PA, O'Reilly BG, Vivion MC. Neomycin ototoxicity: ultrastructural surface pathology of the organ of Corti. Scanning electron microscopy. III. SEM, Inc. Chicago: AMF O'Hare, 1980.

10. Simmons FB. Permanent intracochlear electrode in cats. Tissue tolerance and cochlear microphonics. Laryngoscope 1967; 79:171-83.

11. Michelson RP. The results of electrical stimulation of the cochlea in human sensory deafness. Ann Otol Rhinol Laryngol 1971; 80:914-9.

12. Clark GM, Kranz HG, Minas H, Nathar JM. Histopathological findings in cochlear implants. J Laryngol Otol 1975; 89: 495-504.

13. Clark GM. An evaluation of pre-scalar cochlear electrode implantation techniques. An histopathological study in cats. J Laryngol Otol 1977; 91:185-98.

14. Schindler RA, Bjorkroth B. Traumatic intracochlear electrode implantation. Laryngoscope 1979; 89:752-8.

15. Sutton D, Miller JM, Pfingst BE. Cochlear histopathology. A comparison of two implant designs for chronic use in monkey scala tympani. Ann Otol Rhinol Laryngol 1980; 89 Suppl 66: 11-4.

16. Pfingst BE, Sutton D, Miller JM, Bohne BA. Relation of psychophysical data to histopathology in monkeys with cochlear implants. Acta Otolaryngol (Stockh) 1981; 92:1-13.

17. Guild SR. A graphic reconstruction method for the study of the organ of Corti. Anat Rec 1921; 22:141-57.

18. Schindler RA, Merzenich MM. Chronic intracochlear electrode implantation: cochlear pathology and acoustic nerve survival. Ann Otol Rhinol Laryngol 1974; 83:202-15.

19. Walsh SM, Leake-Jones PA, Vurek L, Merzenich MM. Effects of chronic electrical stimulation of auditory nerve in cat. ARO Meeting, St. Petersburg Beach, Florida, Jan. 1980.

20. Duckert LC, Miller JM. Acute morphological changes in guinea pig cochlea following electrical stimulation: a scanning electron microscope study. Ann Otol Rhinol Laryngol 1982; 91: 33-40.

21. Simmons FB. Electrical stimulation of the auditory nerve in cats. Long term electrophysiological and histological results. Ann Otol Rhinol Laryngol 1979; 88:533-9.

22. Bergstrom L. Some pathologies of sensory and neural hearing loss. Can J Otol 1975; 4 Suppl 4:1-28.

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BRAINSTEM CONDUCTION ABNORMALITIES IN SPASMODIC DYSPHONIA

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Twelve spasmodic dysphonia patients were evaluated by three different auditory brainstem response parameters; 75% were abnormal. Three of the 12 had prolonged wave I-V interpeak latency. Seven had pathologic wave V latency shifts at a high stimulus rate. Amplitude ratios were normal for all subjects. The authors hypothesize that spasmodic dysphonia is a disorder of variable cranial nerve symptom presentations, and offer several possible models to account for its sporadic representation in the nervous system.

Nervous hoarseness, spastic aphonia and stammering of the vocal cords are only a few of the names used to describe the phonatory disorder known as spasmodic (spastic) dysphonia (SD).[1,2] The bizarre vocal patterns, symptom variability, initial reports of female predominance and the lack of therapeutic success led clinicians until recently to ascribe a psychogenic etiology to this disease.[1,2] Although functional theories have dominated spasmodic dysphonia literature over the past century, several authors reported coexistent neurologic signs suggestive of organic disease.[2-5]

As early as 1939, Critchley identified cranial nerve symptoms, such as facial tics and spasmodic torticollis, in three SD patients.[3] Later, Robe prospectively studied ten patients in search of an organic foundation for this disorder.[6] While her 90% incidence of electroencephalographic abnormalities remains unreplicated, she clearly challenged the conventional view which regarded SD as a functional disease. After extensive investigation of SD patients, Aronson et al hypothesized that spastic dysphonia is predominantly a result of central nervous system (CNS) dysfunction, and that psychiatric factors may be viewed as complicating rather than primary.[1] They divided spasmodic dysphonia into two types. The more common and disabling adductor form presents with a tense or "strangled" voice. The abductor disorder is characterized by an involuntary separating of the vocal cords resulting in a breathy voice or aphonia.[7]

Dedo and others have reported successful surgical management of adductor SD based on the paramedian position assumed by the vocal cords after recurrent laryngeal nerve (RLN) sectioning and the compensatory movement by the contralateral vocal fold.[8-11] Histologic evidence to support a peripheral nerve etiology has been offered by Boccino and Tucker[11] and Dedo et al.[12,13] They identified myelinization abnormalities in 30 to 70% of RLN biopsies obtained from patients undergoing RLN section.[11,12] In contrast, Ravits et al refuted the morphologic evidence upon which others had based their claim that peripheral neuropathy was the etiology of this disorder.[14] In view of these conflicting claims and the absence of quantifiable measurements, the basis of the disorder remains open to speculation.

In the past decade, the auditory brainstem response (ABR) has emerged as an important technique for the identification of intracranial pathology. The ABR is a series of 5 to 7 surface-recorded, neurogenic potentials that occur in the first 10 ms following auditory stimulation.[15] It is apparent that wave I reflects activity in the eighth cranial nerve; however, each of waves II-VII represent composite activity from at least two regions in the auditory brainstem.[16,17]

Sharbrough et al used the ABR procedure to evaluate 18 SD patients. Thirty-nine percent manifested brainstem abnormalities as demonstrated by prolonged interwave or interpeak latencies.[18] The present report originated in an attempt to utilize Sharbrough's application of ABR in the evaluation of other patients with spasmodic dysphonia. In addition to the interpeak latency (IPL) measure used by Sharbrough and his colleagues, pathophysiological findings in neurologic diseases can also be obtained from two additional measures: the wave V to wave I amplitude ratio (AR), and the change in wave V latency at high stimulus rates.[19-23]

In order to appreciate the relevance of adding these measures to the ABR test battery, some background information on the otoneurologic variables affecting such measurement is presented here. The

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TABLE 1. PRETREATMENT VOCAL SYMPTOMS ASSOCIATED WITH SPASMODIC DYSPHONIA*

				I-V IPL† *(ms)* *60 nHL, 20/s*		*Repetition Rate Shift of Wave V (ms)* *60 nHL, 90/s*		
	Sex	*Age*	*Duration of Symptoms (yr)*	*L*	*R*	*L*	*R*	*ABR Abnormality*
Patients with adductor disorder								
1	M	48	20	Neg (4.68)	4.70	0.96	0.48	+
2	F	56	5	3.84	4.16	1.60	1.80	+
3§	M	43	20	3.80	Neg	1.52	1.56	+
4	F	56	5	4.04	3.72	0.72	1.16	+
5	F	47	3	4.51	4.08	0.56	1.20	+
6	F	39	2	3.72	3.68	0.72	0.60	—
7§	M	57	3	4.48	Neg (3.80)	0.72	1.16	+
8	M	44	4	3.82	4.00	0.44	0.56	—
9	F	54	6	3.82	3.93	1.26	1.08	+
10	M	42	1	Neg (4.16)	Neg (4.64)	0.96	0.80	+
Patients with abductor disorder								
11§	M	60	4	Neg (4.92)	4.34	0.64	1.24	+
12	F	46	2	3.56	3.40	0.40	0.48	—

*Twelve patients ranked from most to least involved in terms of approximate severity of pretreatment vocal symptoms.

†Interpeak latencies (IPLs) ≥ 4.6 ms and repetition rate shifts > 1.04 ms are abnormal.

§Losses ≥ 35 dB at 4 kHz and above in both ears.

+ Presence of an ABR abnormality; — No abnormality; nHL - Hearing level in normal adult; Neg - Could not identify wave I at 60 dB nHL; ( ) - IPL in ms at 70 dB nHL.

wave I to V IPL reflects neural conduction time from the periphery (wave I) to the rostral brainstem in the region of the inferior colliculus (wave V).[20,22] In general, wave I to wave V IPLs greater than 4.6 ms are pathologic in adults through 50-60 years and in infants over 18 months, regardless of stimulus intensity (Finitzo-Hieber T, unpublished data).[18,20] However, patients with high-frequency hearing loss have diminished wave Is and shortened IPLs.[24] The presence of high-frequency hearing loss therefore will increase the chance of obtaining a false-negative result on the ABR.

The AR is the ratio of wave V to wave I and is used in lieu of absolute amplitude values which exhibit substantial intersubject variability. Amplitude ratios should be greater than a value of 0.5 to be considered normal (Finitzo-Hieber T, unpublished data).[25,26]

The effect of high stimulus rates is the third measurement with neurologic application. Gerling and Finitzo-Hieber found that increasing the stimulus rate from 20 to 90 clicks per second in normal listeners produces a mean wave V latency shift of 0.61 ms (standard deviation = 0.14 ms).[27] They define an abnormal wave V latency increase as greater than three standard deviations above the mean, or greater than 1.04 ms. An analysis of the rate effect in their hearing-impaired patients demonstrated significantly shorter latencies when compared to normal subjects. Once again, with hearing impairment, there is an increased risk of false-negative findings.

When the authors' experimental ABR investigations were combined with an extensive literature review, evidence emerged supporting a view of SD as a CNS disease with variable cranial nerve presentation.[28]

METHODS

Six females and six males diagnosed as having spasmodic dysphonia were studied (Table 1). Ten patients evidenced adductor SD and two abductor SD. Spasmodic dysphonia was independently diagnosed by a minimum of two speech pathologists and one otolaryngologist experienced in the evaluation and management of this disorder. Pure-tone thresholds from 250 through 2,000 were normal limits for 12 patients. Three male subjects (Table 1: 3, 7, 11) exhibited 35 to 75 dB high-frequency losses from 4 to 8 kHz.

Bioelectric activity was recorded from gold cup EEG electrodes placed at the vertex and each mastoid of the patient (Cz to A1 or A2), with vertex and positive indicated by an upward deflection on the oscilloscope. Interelectrode impedance was < 5,000 ohms. The electroencephalographic signal was amplified (10^5) via a Grass P 511 amplifier, filtered (300-3,000 Hz) and fed to a Nicolet

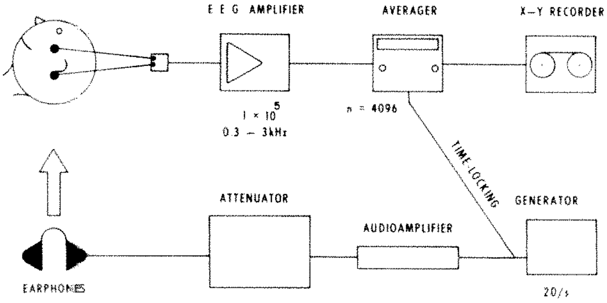

Fig. 1. Representation of auditory brainstem response monitoring and recording equipment.

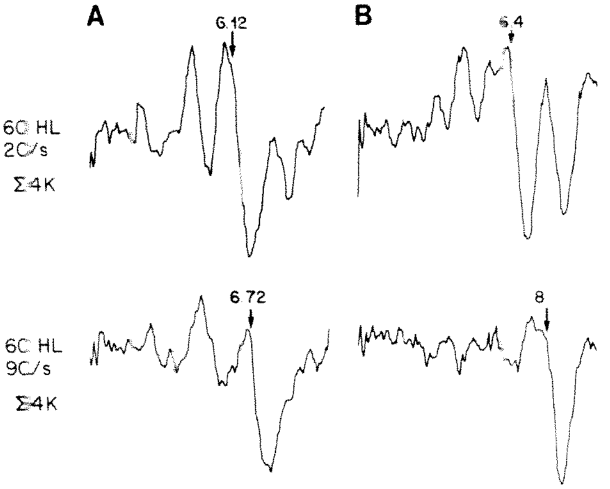

Fig. 2. A) Normal wave V latency shift from 6.12 ms at 20/s (top) to 6.72 ms at 90/s (bottom). The shift in wave V latency at 90/s is 0.6 ms. B) An abnormal wave V latency shift from 6.4 ms (top) at 20/s to 8 ms (bottom) at 90/s. The shift in wave V is 1.6 ms. Wave V latency is measured at the peak farthest to the right which is greater than half the amplitude of the IV-V complex on the downward negative slope. (Vertex positive is indicated by an upward deflection.)

(model 1072) computer averager triggered by stimulus onset (Fig. 1). The time base was 20.48 ms (512 memory addresses at 40 μs per address). Response latency was measured by moving the cursor on the computer averager to the positive peak of the desired component, determining the address in memory of that point, and converting that address to real time by multiplying the address by the 40-μs dwell time. Waveform amplitudes from peak to trough were measured from an oscilloscope display.

The stimulus was a 100-μs rarefaction square wave pulse generated by a Grass S-48 stimulator and delivered monaurally to an electromagnetically shielded earphone (TDH 49). Click intensity was referenced to the average psychophysical click threshold of trained normal listeners in the authors' laboratory. Such clicks at 30 dB above this reference, with an interstimulus interval of 50 ms, produced a sound pressure level (SPL) reading of 67 dB on a measuring amplifier (Brüel and Kjaer model 2606), linear scale, "slow" setting, when delivered through a 6-cc coupler and associated condenser microphone.

Patients were tested while recumbent in a double-walled, soundproof room during natural or sedated sleep. Test sessions generally lasted 1 to 1½ hours. The amplified EEG was monitored continuously on an oscilloscope to control for muscle potential and movement artifacts that might contaminate recordings. Each response represented an average of 2,048 clicks, replicated once and summed for greater accuracy and easier identification. Initial test stimulus was 60 dB hearing level in normal adults (nHL) at 20 clicks per second, followed by 90 clicks per second at the same hearing level.

RESULTS

All three ABR parameters were examined in an effort to document CNS pathology which might not be evident if only one measurement was utilized. The results of the current investigation are summarized in Table 1. Seventy-five percent (9/12) were judged abnormal. This group included 8 of the 10 adductor and 1 of the 2 abductor SD patients. Three patients had prolonged central conduction time as measured by wave I-V IPL (≥4.6 ms). Seven had pathologic wave V latency changes at the high stimulus rate (Fig. 2). Of these, three patients showed this change bilaterally and four unilaterally. Patient 11 (Table 1) demonstrated an IPL abnormality in one ear and a rate abnormality in the other ear. No amplitude ratio abnormalities were identified for any patient.

Of the 12 patients studied, 3 had both abnormal brainstem changes and high-frequency hearing loss. Since high-frequency hearing loss may complicate the otoneurologic interpretation of the ABR, some comment on these three patients is appropriate. Patient 3 had prolonged rate changes bilaterally; patient 7 had a prolonged rate change in his right ear; and patient 11 had a 1.24 ms rate increase right, and a 4.92 ms IPL left (Table 1). As expected, IPL measurements were difficult to obtain in these patients because of their high-frequency impairments. Wave I is highly dependent on the integrity of the basal turn of the cochlea, and thus its amplitude can be markedly diminished with a high-frequency impairment. We are comfortable with labeling these patients as abnormal, because while the complication of high-frequency hearing loss may result in false-negative findings, it should not produce false-positive findings.[24,27]

DISCUSSION

Coincidental evaluation of the auditory system in SD patients is not a unique idea. Following the earlier work of McCall,[29] Hall and Jerger[30] applied acoustic reflex measurements to six well-studied patients. They found a prolonged contraction time, and note the work of Borg which suggests this finding is indicative of central reflex pathway pathology.[31]

In the present study, 12 patients with SD were evaluated by ABR. Of 9 patients who demonstrated abnormalities, 7 had prolonged wave V latency shifts at the high stimulus rate. The authors inter-

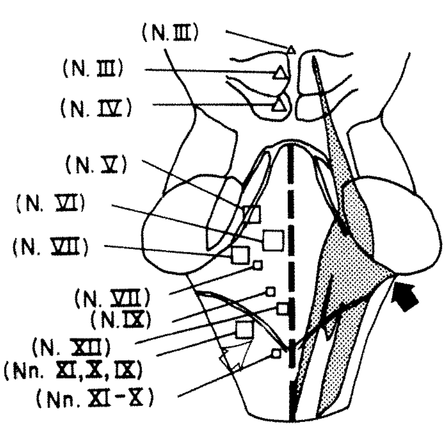

Fig. 3. Schematic of brainstem showing efferent nuclei on the left side of the figure and afferent on the right. Theoretical lesion might involve nucleus ambiguous (CN X, open arrow) and auditory area (CN VII, closed arrow). N. - Nerve; Nn. - Nerves. (Modified from Crosby EC, Humphrey T, Lauer EW. Correlative anatomy of the nervous system. New York: McMillan, 1962:131.)

TABLE 2. ASSOCIATED CRANIAL NERVE (CN) SYMPTOMS REPORTED WITH SPASMODIC DYSPHONIA

Presumed CN	*System or Structure*	*Symptoms*	*Cases*	*Ref.*
X	Larynx			
	Vocal folds	Phonatory spasms	100%	All
		Expiratory spasm	2/2	40
			?/8	32
		Phonatory tremor	?/8	32
			1/1	41
			18/31	2
			14/27	1
	Ventricular folds	Phonatory spasm	2/2	40
			?/8	32
		Expiratory spasm	1/2	40
			?/8	32
	Pharynx	Constriction	1/2	40
			?/8	32
		Tonic spasms, tremors	?/8	32
	Palate (IX?)	Spasms	1/3	3
			?/8	32
		Tremor	?/8	32
		Asymmetry	1/27	1
	Cardiopulmonary system	Tachycardia attacks	1/1	41
	Digestive tract	Choking sensation	?	33
		Dysphagia	1/10	6
	Histopathology of RLNs	Abnormalities indicative of demyelination	30%	12
			14-18	11
VIII	Auditory system	Abnormal ABR, interpeak latencies (IPL)	7/18	18
		IPL and prolonged latencies at high stimulus rates	5/6	28
		Vertigo	1/10	6
		Acoustic reflex, prolonged contraction	6/6	30
XI	Neck			
	Anterior	Ticlike contractions or spasms	?	1
			?	3
			most/12	34
	Posterior	Spasmodic torticollis	1/27	1
			1/3	3
			1/1	36
XII	Tongue	Spasmodic movements, clonic movements, fibrillary tremors*	1/3	3
		Unilateral protrusion*	1/10	6
		Reduced alternate motion (poor diadochokinesis)	3/27	1
			1/2	40
VII	Face	Tics, twitches or spasms†	8/27	1
			2/2	42
			1/1	37
		Grimacing or wrinkling forehead*	most/12	34
			1/2	40
			2/2	42
		Weakness	1/3	3
			1/10	6
		Asymmetry	5/10	6
		Synkinesis	1/27	1
			2/2	42
	Lips	Movements§	?	1
		Myoclonic movements	1/3	3
	Cheek	Buccolingual dyskinesia	1/2	34
	Eye	Blepharospasm	1/2	34
			1/1	37
		Eye blinking	?	1
		Tremor of eyelid	1/10	6
		Ptosis	1/27	1
V	Jaw	Jerking up and left, lateral tremor*	1/3	3
		Retraction	1/1	37
		Increased reflex	3/27	1
		Poor diadochokinesis	1/2	40
II	Visual system	Pallor of optic discs	1/3	3
			1/10	6
III		Left pupil larger than right	2/10	6
III, IV, VI		Nystagmoid movements	1/10	6
II		Transient scotomata	1/10	6

*With phonation.

†Stated as facial or tongue twitches.

§With laryngeal spasms.

pret this finding as indicative of dysfunction which is apparent only when the auditory brainstem pathway is stressed. This less efficient CNS transmission exceeds the normal adaptation that occurs at high stimulus rates, and might result from a reduction in the number of auditory fibers present or altered synaptic function. A second ABR abnormality, increased wave I-V interpeak latency, was identified in three patients using the criterion of ≥4.6 ms. The prior ABR investigation by Sharbrough et al found 39% SD patients to have abnormal IPL.[18] Applying only their IPL criterion to the patients reported herein would have led to identification of 42% (5/12) as abnormal. Hence, these results are in close agreement.

Interpretation of the vocal symptoms of SD patients as evidence of dysfunction in cranial nerve X and the results of the ABR investigations as clearly showing dysfunction in the auditory pathway, led the authors to ask two questions. First, if SD is viewed as more than an isolated phonatory disorder, is there evidence of other concurrent vagal dysfunction? Secondly, are other cranial nerves affected?

A survey of the SD literature reveals scattered reports of associated nervous system disease in these patients (Table 2). With regard to the first question, there are limited reports of nonlaryngeal, vagal somatic findings. These include phonatory and expiratory tremors, spasms and other atypical movements of the palate and pharynx.[32-34] Such reports may imply that in some SD patients, the vagal dysfunction evident at the vocal folds is only part of a broader disease process. While the reports of cardiopulmonary or digestive symptoms are also limited, they are provocative as indicating visceral efferent vagal pathology and are worthy of consideration.[33] Further research in this area is now in progress.

In addressing the second question, multiple cranial involvement is well documented with motor symptoms predominanting (Table 2). Embedded throughout the literature are intriguing reports of the co-occurrence of SD with other low-incidence pathologies, including essential tremor, spasmodic torticollis, and blepharospasm.[1,3,34-38] Sensory abnormalities are infrequently reported. However, the ABR model might be extended to examine visual and somatosensory evoked potentials in SD patients to objectively evaluate other sensory systems. Further, no patient manifested the full spectrum of potential cranial nerve symptoms. Rather, the pattern of presentation is idiosyncratic, the common symptom being the vocal disorder.

Although highly speculative and perhaps premature, the authors hypothesize that spasmodic dysphonia is a disease involving multiple cranial nerves with variable presentation. It may prove to be one of a family of disorders which are known by different names depending on their site of dysfunction. Therefore, one patient might have concurrent spasmodic torticollis, while another, blepharospasm with or without SD. Such a "patchy" involvement of the nervous system could explain why 25% of the patients in the current report had no abnormalities on ABR. Three disease processes might account for this neurologic pattern. The first possibility is a series of sporadic lesions at the peripheral nerve level. Although the work of Dedo supports this concept, both Ravits' investigations and the evidence reported herein are to the contrary.[12-16] The other two possible pattern models assign the disease site to the brainstem and therefore agree with the ABR results. One of these possibilities might be a "shared" lesion involving variable regions of adjacent cranial nerve nuclei. Whereas, the other process would be a series of sporadically isolated or "skip" lesions within the brainstem nuclei (Fig. 3). At this time, there is no evidence to support one particular pattern of CNS involvement. If SD is viewed as more than a disease of one cranial nerve, then other spasmodic cranial nerve syndromes might represent similar pathology in their appropriate nerve.[39] Perhaps a common pharmacologic agent will control "these spasmodic disorders." A careful and systematic search for multiple cranial nerve involvement in these various disorders will be needed to clarify this matter.

Finally, more information is required to elucidate the natural history of SD patients. Future investigation should include a survey of the progression of SD and its role in conjunction with other manifestations of neurogenic disease as a cause of death of afflicted patients. Then, hopefully, the etiology and treatment for SD might become evident.

REFERENCES

1. Aronson AE, Brown JR, Litin EM, Pearson JS. Spastic dysphonia. I. Voice, neurologic and psychiatric aspects. J Speech Hear Disord 1968; 33:203-18.

2. Aronson AE, Brown JR, Litin EM, Pearson JS. Spastic dysphonia. II. Comparison with essential (voice) tremor and other neurologic and psychogenic dysphonias. J Speech Hear Disord 1968; 33:219-31.

3. Critchley M. Spastic dysphonia ("inspiratory speech"). Brain 1939; 62:96-103.

4. Brodnitz FS. Spastic dysphonia. Ann Otol Rhinol Laryngol 1976; 85:210-4.

5. Furstenburg AC. Evidence of laryngeal participation in emotional expression: its relation to hysterical aphonia. Ann Otol Rhinol Laryngol 1958; 67:516-27.

6. Robe E, Brumlik J, Moore P. A study of spastic dysphonia. Laryngoscope 1960; 70:219-45.

7. Aronson AE. Audio seminars in speech pathology: psychogenic voice disorders. Philadelphia: WB Saunders, 1973.

8. Dedo HH. Recurrent laryngeal nerve section for spastic dysphonia. Ann Otol Rhinol Laryngol 1976; 85:451-9.

9. Biller HF, Som ML, Lawson W. Laryngeal nerve crush for spastic dysphonia. Ann Otol Rhinol Laryngol 1979; 88:531-2.

0. Barton RT. Treatment of spastic dysphonia by recurrent laryngeal nerve section. Laryngoscope 1979; 89:244-9.

1. Bocchino JV, Tucker HM. Recurrent laryngeal nerve pathology in spasmodic dysphonia. Laryngoscope 1978; 88:1274-80.

2. Dedo HH, Townsend JJ, Izdebski K. Current evidence for the organic etiology of spastic dysphonia. ORL 1978; 86:875-80.

3. Dedo HH, Izdebski K, Townsend JJ. Recurrent laryngeal nerve histopathology in spastic dysphonia. Ann Otol Rhinol Laryngol 1977; 86:806-12.

4. Ravits JM, Aronson AE, DeSanto LW, Dyck PJ. No morphometric abnormality of recurrent laryngeal nerve in spastic dysphonia. Neurology 1979; 29:1376-82.

5. Jewett D, Williston J. Auditory evoked far fields averaged from the scalp of humans. Brain 1971; 94:681-96.

6. Buchwold J, Huang CM. Far-field acoustic responses: origins in the cat. Science 1975; 189:382-4.

7. Achor J, Starr A. Auditory brain stem responses in the cat. II. Effects of lesions. Electroencephalogr Clin Neurophysiol 1980; 48:174-90.

8. Sharbrough FW, Stockard JJ, Aronson AE. Brainstem auditory evoked responses in spastic dysphonia. Trans Am Neurol Assoc 1978; 103:198-201.

19. Starr A, Achor J. Auditory brainstem responses in neurological disease. Arch Neurol 1975; 32:761-8.

20. Starr A. Clinical relevance of auditory brainstem responses in brainstem disorders in man. In: Desmedt J, ed. Progress in clinical neurophysiology. Vol. 2. Basel: Karger, 1977:45-57.

21. Stockard J, Rossiter V. Clinical and pathologic correlates of brainstem auditory response abnormalities. Neurology 1977; 27:316-25.

22. Hecox K, Cone B, Blau M. Application of the brainstem auditory evoked responses to the diagnosis of pediatric neurological diseases. Neurology 1981; 31:832-40.

23. Pratt H, Ben-David Y, Peled R, Podoshin R, Scharf B. Auditory brainstem evoked potentials: clinical promise of increasing stimulus rate. Electroencephalogr Clin Neurophysiol 1981; 51:80-90.

24. Coats A, Martin J. Human auditory nerve action potentials and brainstem evoked responses: effects of audiogram shape and lesion location. Arch Otolaryngol 1977; 103:605-22.

25. Starr A, Hamilton AE. Correlation between confirmed sites of neurological lesions and abnormalities of far-field auditory brainstem responses. Electroencephalogr Clin Neurophysiol 1976; 41:595-608.

26. Starr A, Sohmer H, Celesia G. Brainstem auditory evoked potentials in neurology: methodology, interpretation, clinical application. In: Aminoff MJ, ed. Electrophysiologic approaches to neurologic diagnosis. New York: Churchill Livingston, 1979: 541-67.

27. Gerling I, Finitzo-Hieber T. Auditory brainstem response with high stimulus rates in normal and patient populations. Ann Otol Rhinol Laryngol 1982 (in press).

28. Finitzo-Hieber T, Freeman FJ, Gerling IJ, Schaefer SD. Auditory brainstem response abnormalities in patients with adductor spasmodic dysphonia. Am J Otolaryngol 1982 3:26-30.

29. McCall G. Acoustic impedance measurement in the study of patients with spasmodic dysphonia. J Speech Hear Disord 1973; 38:250-5.

30. Hall J, Jerger J. Acoustic reflex characteristics in spastic dysphonia. Arch Otolaryngol 1976; 102:411-5.

31. Borg E. On the neuronal organization of the acoustic middle ear reflex: a physiological and anatomical study. Brain Res 1973; 49:101-23.

32. McCall GN, Skolnick ML, Brewer DW. A preliminary report of some atypical movement patterns on the tongue, palate, hypopharynx and larynx of patients with spasmodic dysphonia. J Speech Hear Disord 1971; 36:466-70.

33. Rabuzzi D, McCall G. Spasmodic dysphonia: a clinical perspective. Trans Am Acad Ophthalmol Otolaryngol 1972; 76:724-8.

34. Aminoff MJ, Dedo HH, Izdebski K. Clinical aspects of spasmodic dysphonia. J Neurol Neurosurg Psychiatry 1978; 41:361-5.

35. Aronson AE. Clinical voice disorders. New York: Thieme-Stratton, 1980.

36. Wilson F, Olding DJ, Mueller K. Recurrent laryngeal dissection: a case report involving return of spastic dysphonia after initial surgery. J Speech Hear Disord 1980; 45:112-8.

37. Jocome DE, Yanez GF. Spastic dysphonia and Meige disease. Neurology 1980; 30:349.

38. Izdebski K, Shipp T, Dedo HH. Predicting postoperative voice characteristics of spastic dysphonia patients. Otolaryngol Head Neck Surg 1979; 87:428-34.

39. Matthews WB, Beasley P, Jones WP, Garland G. Spasmodic torticollis: a combined clinical study. J Neurol Neurosurg Psychiatry 1978; 41:485-92.

40. Parnes SM, Lavorato AS, Myers EN. Study of spastic dysphonia using videofiberoptic laryngoscope. Ann Otol Rhinol Laryngol 1978; 87:322-6.

41. Fox DR. Spastic dysphonia: a case presentation. J Speech Hear Disord 1969; 34:275-9.

42. Schnitzler J. Klinischer-Atlas der laryngologie nebst Anleitung zur diagnose und therapie der Krankheiten des Kehlkopfes und der Luftrohre. Leipzig: Branumuller, 1896.

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ECTOPIC GASTRIC MUCOSA IN THE UPPER ESOPHAGUS AS A CAUSE OF DYSPHAGIA

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A rare case of dysphagia, caused by ectopic gastric mucosa situated in the upper esophagus, is reported.

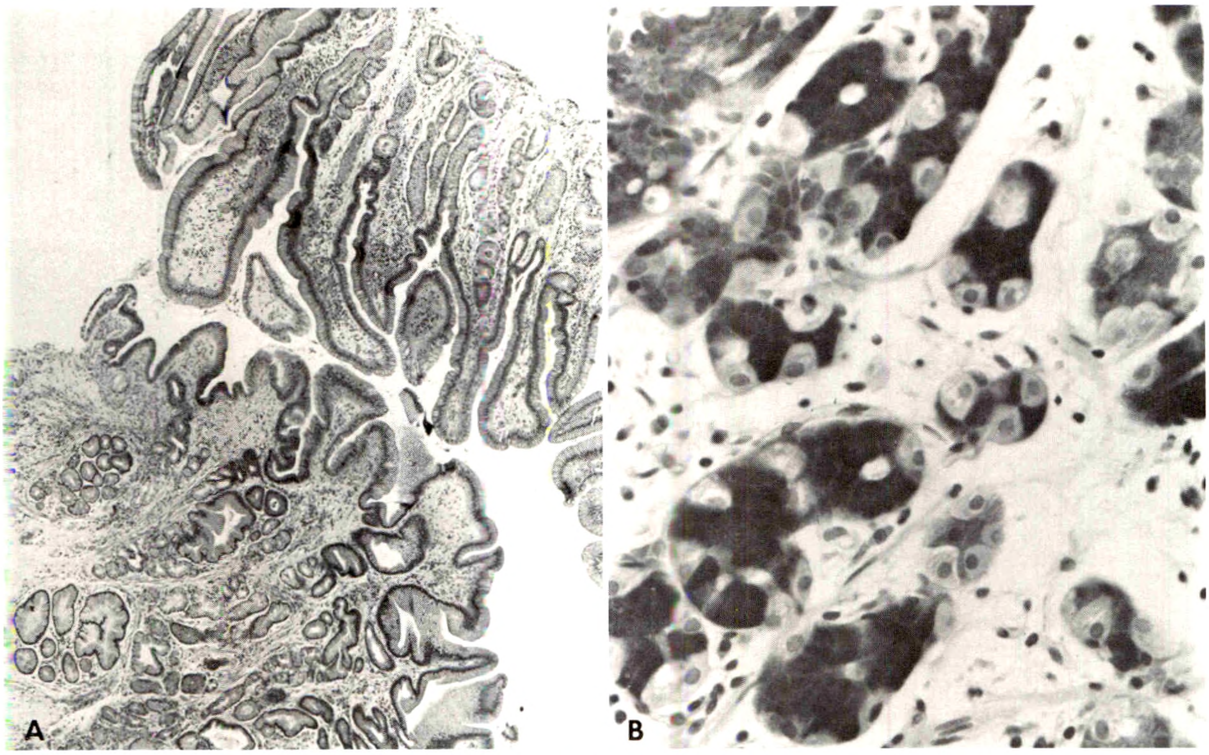
Dysphagia caused by ectopic gastric mucosa in the upper esophagus is a rare condition. It appears to have been first reported by Foxen,[1] and no further cases seem to have been described.

CASE REPORT

A 31-year-old male presented with a 7-month history of progressive dysphagia. He indicated that there was discomfort in the lower neck when eating solids. There were no other symptoms related to his ears, nose, or throat. A general systemic inquiry was not helpful, apart from revealing that he was smoking 40 cigarettes a day. No abnormalities were detected on clinical examination.

Investigations. Routine hematological and biochemical investigations were normal, as was the chest x-ray film. A barium swallow was performed and showed a constant filling defect at the level of the first thoracic vertebra. The lower esophagus, stomach, and duodenum were normal. No gastric reflux was demonstrated.

An esophagoscopy was carried out which revealed the presence of an inflamed-looking sessile lesion, about 1 cm in diameter, arising from the anterior esophageal wall. The site of the lesion corresponded with the filling defect noted on the barium swallow x-ray film. No abnormality of the cricopharyngeus or the remainder of the esophagus were noted, and a total macroscopic removal of the lesion was attempted. Following this, no further



A) Photomicrograph of esophageal biopsy showing similar structure to gastric mucosa as found in cardiac region. Mucous secretory surface epithelium seen within underlying groups of glands separated by upward extensions of fibers of muscularis mucosae (H & E, x35). B) Magnifications of glands as seen in A showing pale rounded parietal cells with central nucleus and darker chief cells (PAS, x 330).

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dysphagia was reported by the patient, and he remains asymptomatic after seven months.

HISTOLOGY

Histological examination showed the presence of gastric mucosa of the cardiac type, consisting of mucus-secreting epithelium lining the surface and crypts. There was no stratified squamous epithelium. The underlying mucous glands and focal groups of glands contained parietal and chief cells. There were also small areas in which goblet cells were present in the surface and crypt epithelia. These areas were associated with a minor increase in chronic inflammatory cells in the lamina propria, together with a small number of polymorphonuclear leukocytes (Figure). The Figure also shows a higher power section of glandular tissue showing parietal and chief cells.

DISCUSSION

The esophageal mucosa is normally lined by stratified squamous epithelium. However, areas of columnar epithelium are found fairly frequently during routine postmortem examinations. Schridde[2] found areas of ciliated columnar epithelium in 70% of 30 such cases. In 1,000 consecutive pediatric autopsies, Rector and Connerly revealed the presence of heterotopic gastric mucosa in 7.8% of the cases.[3] Over half were in the upper third. All cases were asymptomatic during life.

Embryologically, the esophageal mucosa is initially covered by columnar epithelium which becomes replaced by stratified squamous epithelium. This transition begins in the middle of the esophagus. Incomplete development would account for the presence of the columnar epithelium, but it is difficult to explain the related presence of ectopic gastric glands. Again, it is probably a congenital anomaly during the development of the stomach. As the latter is first found in the midneck region, cell nests may be left during its "descent."

Whatever the process, it is interesting to note that this not uncommon portmortem finding is usually not responsible for clinical symptoms.

The present case differs slightly from that reported by Foxen.[1] In his case, dysphagia was thought to be due to spasm of the cricopharyngeus, the latter being attributed to the presence of ectopic gastric mucosa in the cervical esophagus.

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REFERENCES

1. Foxen EHM. Ectopic gastric mucosa in the cervical oesophagus, a possible cause of dysphagia. J Laryngol Otol 1957; 71:419-23.

2. Schridde H. Uber Magenschleimhaut-Inseln vom Bau der Cardialdrüsenzone und Fundusdrüsenregion und den unteren, oesophagealen Cardialdrüsen gleichende Drüsen im obersten Oesophagusabschnitt. Virchows Arch Pathol Anat 1904; 175: 1-16.

3. Rector LE, Connerley ML. Aberrant mucosa in the esophagus in infants and children. Arch Pathol 1941; 31:285-94.

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EVALUATION OF THE NEGATIVE PRESSURE SUCTION METHOD IN THE CYTODIAGNOSIS OF NASOPHARYNGEAL CARCINOMA

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A special device for collecting exfoliative cells in nasopharyngeal carcinoma diagnosis by negative pressure suction method is recommended. This device consists of a metallic suction tube with a round tip and a modulator which is connected to a suction pump; it passes via the oral cavity into the nasopharynx to collect exfoliative cells. From March 1973 to July 1977, 824 out-patients were examined with cytology and biopsy in our hospital. Of these, 481 cases were confirmed as nasopharyngeal carcinoma. Among them, 431 were cytology-positive; 453 cases were biopsy-positive. The positive cytology rate was 89.6% and the positive biopsy rate was 94.2%.

INTRODUCTION

Since Morrison first utilized cytologic diagnosis in nasopharyngeal carcinoma (NPC) in 1949, various devices have been employed to collect cells from the nasopharynx in an attempt to increase diagnostic accuracy. Since the accuracy of cytologic diagnosis is so low, it cannot be used clinically as a routine procedure for NPC diagnosis (see table). In 1973 we designed a negative pressure suction method for cytologic examination.[1,8,9]

MATERIALS AND METHOD

A metallic suction tube with a stainless steel tip is connected to a suction pump. The tip, which is round in appearance, has 15-18 small openings on its wall. A small piece of fine cloth is inserted into this tip before it is screwed onto the tube. After suction, the exfoliative cells will be found collected on this cloth, which is then used for smearing. A modulator valve on the tube acts as a switch for adjusting the negative pressure during the suctioning process and is provided with a piston. Rotation of the piston changes the size of the opening, and this in turn affects the patency of the suction tube (Figs. 1 and 2).

Before manipulation is undertaken, the nasopharynx is ordinarily anesthetized by spraying it with 1% dicaine. The suction tube is then passed through the oral cavity into the nasopharynx. The tip of the suction tube should contact the tumor mass or its infiltrated tissue. Negative pressure used for suction is not more than 30 mm/Hg in most cases. Some blood streaks may be found in the saliva immediately following suctioning, but no pain is experienced, except a sort of discomfort.

Manipulation of the suction instrument is first carried out under the guidance of a headmirror and a small postnasal mirror. After several times, the process can be carried out without illumination.

As soon as the suction tube is withdrawn, the tip is removed and the cloth taken out. Numerous exfoliative cells will be found collected on this cloth, usually a sufficient number for smearing. Generally 3 to 5 smears are needed for each examination. Cytosmears are then fixed with a few drops of absolute alcohol and then stained with Papanicolaou technique or hematoxylin and eosin.

RESULTS

Those patients under suspicion of NPC or chronic nasopharyngitis were given cytologic examinations and biopsies were performed on the nasopharynx. When the biopsy was positive and the cytology was negative, no further cytologic examination was required. If the cytology was positive, however, and the biopsy was negative, and the clinical picture did not support the diagnosis, a biopsy would then be repeated. When the cytology and biopsy were both negative, but there existed strong clinical evidence of NPC, both exfoliative cells and biopsy were reexamined.

During the period March 1973 to July 1977, 824 out-patients were examined. Of this number, 481 cases were confirmed NPC. Cytology and biopsy were both positive in 403 cases; positive cytology with negative biopsy was found in 28 cases; and negative cytology with positive biopsy occurred in 50 cases. Among 481 cases of confirmed NPC, 431 cases were cytology-positive, for a positive cytology rate of 89.6%; 453 cases were biopsy-positive, for a positive biopsy rate of 94.2% ($p<0.05$). A false negative rate in our cytologic diagnosis was found in 50 cases, but no false positive rate was found.

COMMENT

Nasopharyngeal carcinoma is derived from the epithelium of the nasopharyngeal mucosa. The tumor mass develops in the nasopharynx and is often manifested as a nodule, granulation tissue, ulceration or a cauliflower-like infiltration. Abundant cancer cells are exfoliated and are found in the nasopharyngeal secretion, which is essential for cytologic examination. Early cases of NPC, even carcinoma in situ, can be easily detected by cytologic examination.

Our negative pressure suction method can collect an extensive amount of exfoliative cells, especially from the fossa and hidden places in the nasopharyngeal cavity. In addition, even those cancer cells within the infiltrated carcinomatous tissue, although not exfoliated, can still be obtained by

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ANALYSIS OF THE ACCURACY OF CYTOLOGIC DIAGNOSIS IN NPC AS PERFORMED BY DIFFERENT AUTHORS, 1949-1964[2-7,10]

Nationality	*Authors*	*Biopsy-Positive Cases*	*Cytology-Positive Cases*	*Corresponding Rate of Cytology-Positive to Biopsy-Positive Cases*
USA	Morrison (1949)	8	7	—
USA	Hopp (1958)	12	11	—
PRC	Ma & Cheng (1958)	63	24	38.1
Indonesia	Djojopranoto (1960)	23	6	26.1
PRC	Wang Yi Ling (1963)	146	89	61.0
PRC	Liang Be Chung (1964)	77	46*	60.0
Singapore	Ali & Shanmugaratnam (1964)	79	35	44.3
PRC	Sheng Rhin Ying (1964)	74	56	75.7
PRC	Lee Chie (1964)	50	44*	88.0

PRC - People's Republic of China.

*Dissected tumor tissue blocks used to make cytosmears in some cases.

means of this method. This is the reason our method can obtain a high positive cytology rate. On the other hand, we attribute a false negative rate in our cytologic diagnosis to the following conditions.[11]

1. Different surgeons in our clinic collected samples. At the beginning they were not thoroughly familiar with the manipulation of the suction method. During suctioning, the tip of the tube should be in contact with the tumor mass or infiltrated tissue, otherwise a negative cytology ensues. Examination of the nasopharynx immediately after suctioning is an important measure in determining the success of sample collection. When the tip of the suction tube is in contact with the tumor mass, there will be a bloody secretion sticking on the mass thereafter. If the tip does not touch the mass or the infiltrated tissue, we repeat the suction at once. Cytosmears were fixed immediately after suctioning with absolute alcohol since delay would cause autolysis of the exfoliated cells.

2. Cytologic diagnosis is difficult with infection (granulation tissue), necrosis and the presence of blood on the tumor mass. During suctioning large pieces of devitalized tissue or blood clots are collected. Cancer cells are relatively scanty throughout the sample, and this is the reason for some of our false negative cases.

3. In two thirds of the cytologically positive cases, the cancer cells collected by our method were abundant; these cases can therefore be easily diagnosed. Cancer cells were less abundant in the remaining one third of the cytologically positive cases; however, in this group typical cancer cells can still be found after careful scrutiny by experienced cytologists and the cancer can be diagnosed in the majority of them. In those exceptional cases where cytologic diagnosis is difficult, consultation or reexamination may be needed to confirm the diagnosis.

4. In rare cases, NPC will not develop or protrude into the nasopharynx in the accustomed manner. Instead, it develops and infiltrates below the mucosa or even into the deeper structures with a smooth and intact mucosa, such as in Rosenmueller fossa. Suctioning with an inadequate force usually results in false negative cases.

In our experience, the following are some advantages in utilizing the negative pressure suction method in cytodiagnosis of NPC.

1. Accuracy of cytologic diagnosis using the method we describe is so high that it is almost the same as the positive biopsy rate.

2. Manipulation of the suction tool causes less pain and discomfort than the biopsy procedure.

3. Preparation and examination of the cytosmear is a much simpler process than that required for the pathologic biopsy specimen. It takes about one hour to perform the cytologic diagnosis.

4. Exfoliative cytology of the suction method can be used in the mass screening for NPC. In October 1973, a mass screening of a commune was undertaken. Of 21,439 rural inhabitants examined, 1132

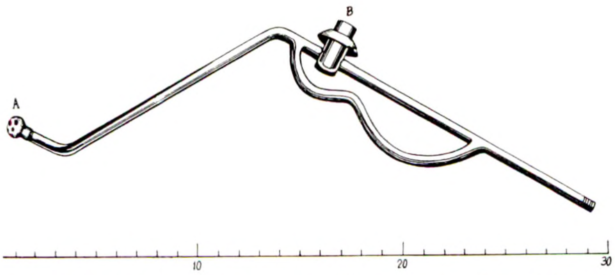

Fig. 1. Negative pressure suction tube. A - Round tip; B - Modulator valve.

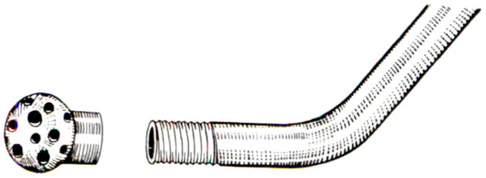

Fig. 2. Round tip of the suction tube.

cytologic examinations were performed with successful results. Ten early cases of NPC were detected.

From 1976 to date, this negative pressure suction method has been utilized in our hospital instead of performing biposies. However, when cytologic examination is negative but clinical evidence is strongly suspicious of NPC, biopsy will then be used to confirm the diagnosis.

REFERENCES

1. NPC Research Group. Cytologic diagnosis of nasopharyngeal carcinoma with exfoliative cells collected by suction. Chinese Med J 1977; 3:69-70.
2. Ali MY, Shanmugaratnam K. Cytodiagnosis of nasopharyngeal carcinoma. Acta Cytol 1967; 11:54-60.
3. Marcuse MP. Diagnostic pathology in gynecology and obstetrics. New York and London: Hoeber Medical Division, 1966; 23.
4. 李琦，安山长：鼻咽癌的脱落细胞学诊断及放射治疗后的细胞学观察，中华耳鼻喉科杂志 10：127，1964。
5. 沈云英等：鼻咽脱落细胞学在鼻咽癌诊断上的应用，福建省肿瘤论文选编 189 页，1964。
6. 王毅鹏，刘同康：鼻咽涂片 203 例的分析，天津医学杂志，肿瘤学副刊 1(4)：224，1963。
7. 梁伯强等：鼻咽癌的组织学类型，生物学特征和组织发生学的研究，肿瘤研究论文集 88 页，中国医学科学院编，上海科学技术出版社，1962。
8. 湛江医学院鼻咽癌协作组：负压吸引脱落细胞检查法诊断鼻咽癌，中华医学杂志，1：45，1976。
9. 湛江医学院鼻咽癌协作组：负压吸引脱落细胞学检查在鼻咽癌诊断上的应用价值，湛江医学院附属医院医药资料选编 1：1，1977。
10. 湛江医学院鼻咽癌协作组：负压吸引脱落细胞学诊断法在鼻咽癌诊断上的探讨，肿瘤防治资料 1：1，1974。
11. 湛江医学院病理学教研组：鼻咽脱落细胞学诊断鼻咽癌的进一步探讨，湛医通讯，科研资料汇编。54 页，1979 年。

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TENTH ANNIVERSARY CONFERENCE ON COCHLEAR IMPLANTS: AN INTERNATIONAL SYMPOSIUM

The Tenth Anniversary Conference of the International Symposium on Cochlear Implants will be held June 22-24, 1983, at the University of California in San Francisco. For further information write or call: Extended Programs in Medical Education, University of California School of Medicine, Room 569-U, Third and Parnassus, San Francisco, CA 94143; (415) 666-4251.

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MORPHOLOGICAL ALTERATIONS AFFECTING THE MICROVASCULATURE IN NASAL ALLERGY

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The fine structure of human nasal blood vessels was studied in 15 nasal allergic patients. Biopsies were taken at different stages after provocation. In the early stage (two minutes after provocation), characteristic alterations of capillaries and venules were congestion, gap formation between two endothelial cells, and swollen vascular endothelial cells. Evidence of locally increased vascular permeability and congestion causing mucosal edema was found. In the late stage (20 minutes after provocation), evidence of congestion disappeared. Vascular dilatation and marked interendothelial cell gaps were observed. In both perivascular space and sometimes in intravascular space, degranulated eosinophils were observed, suggesting that not only histamine but also lysosomal enzymes in eosinphil granules may be involved in causing increased vascular permeability.

Edema of the lamina propria of the nasal mucosa is observed in nasal allergy. The edematous fluid apparently leaks through the vessels which have been altered by allergic reaction. Since the vascular permeability of normal nasal mucosa is greater than that of other organs,[1-3] it is difficult to attribute the tissue edema to greater vascular permeability alone. Alterations in the microvasculature may be important to understanding nasal allergy (immediate hypersensitivity), because this vessel system reveals the possible mechanism of inflammatory response. Some researchers have previously reported on ultrastructural vascular changes in nasal allergy.[4,5] The present study is concerned primarily with the vascular response in different stages after provocation.

METHOD

Biopsies were made of mucosa on the inferior turbinates in 15 patients who reacted to Japanese cedar in skin and nasal provocation tests. The patients ranged in age from 18 to 40 years. Biopsies were taken during the pollen season. Biopsies of the nasal mucosa from eight patients were taken two minutes after provocation and from another seven patients 20 minutes after provocation. A single spray of cedar pollen on the nasal mucosa was the method of provocation. Under local anesthesia (0.5 cc of 0.5% procaine), biopsies were taken with small forceps from the anterior tip of the inferior turbinate. Small blocks were fixed for two hours by immersion in ice-cold 2% glutaraldehyde buffered with 0.1 *M* cacodylate, pH 7.3. Following fixation with glutaraldehyde, the tissue blocks were immersed in 0.1 *M* cacodylate for ten minutes and then postfixed for one hour at room temperature in 2% OsO_4 buffered with 0.1 *M* cacodylate, pH 7.3. The blocks were then dehydrated with ethanol and embedded in Epon 812. Ultrathin sections were treated with uranyl acetate and lead to enhance contrast for electron microscopy.

RESULTS

Two Minutes after Provocation. The superficial vessels underwent changes characteristic in nasal allergy. Prominent among these was congestion. Loss of plasma and tight intravascular packing of erythrocytes were observed (Fig. 1). Edema of the lamina propria of the mucosa was invariably present. Large gaps were occasionally observed between adjacent endothelial cells, and in several capillaries, erythrocytes and eosinophils extravasated into the perivascular space through these gaps (Fig. 1). Greatly swollen endothelial cells were observed in four cases (50%), especially beneath the exfoliated epithelial cells, and to a lesser extent beneath the intact epithelial cell lining. The extent of individual endothelial cell damage varied considerably, and, when slight, consisted of small focal zones of cytoplasmic lucency (Fig. 2A). When damage was more extensive, these cells exhibited a larger zone of extreme cytoplasmic lucency (Fig. 2B). Swollen endothelial cells encroached on the vascular lumina, which frequently were reduced to slit-like spaces containing little plasma (Fig. 2B). Damaged endothelial cells sometimes appeared; however, occlusion of vessels by these cells was relatively infrequent, and platelet sticking and thrombus formation were not observed.

Twenty Minutes after Provocation. Edema of the lamina propria of the mucosa appeared prominently. Vascular dilatation and extreme gap formation between two endothelial cells were observed (Fig. 3A). As very few erythrocytes and a large volume of plasma were observed in the vascular lumen, it was considered that congestion had lessened and blood flowed in the vessel. It was postulated that a great deal of plasma leaked into the perivascular space through gaps (Fig. 3A).

Degranulated eosinophils were observed in both perivascular and intravascular spaces (Fig. 3). The presence of degranulated eosinophils in the intravascular space suggested that the allergen invaded

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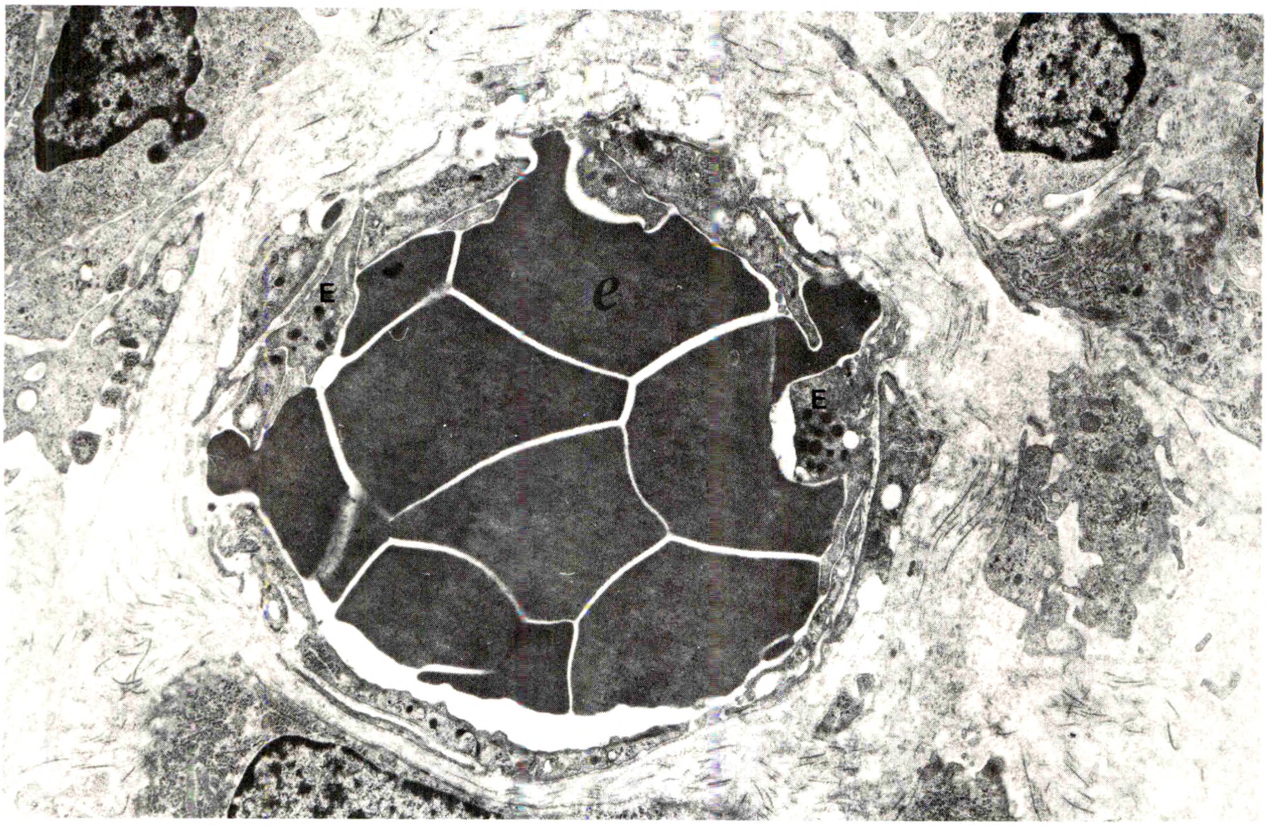

Fig. 1. Superficial capillary showing gap formation between two endothelial cells and congestion at two minutes after provocation. Erythrocytes and eosinophils extravasated into perivascular space through endothelial gaps. E - Eosinophil; e - Erythrocyte. (x6,000)

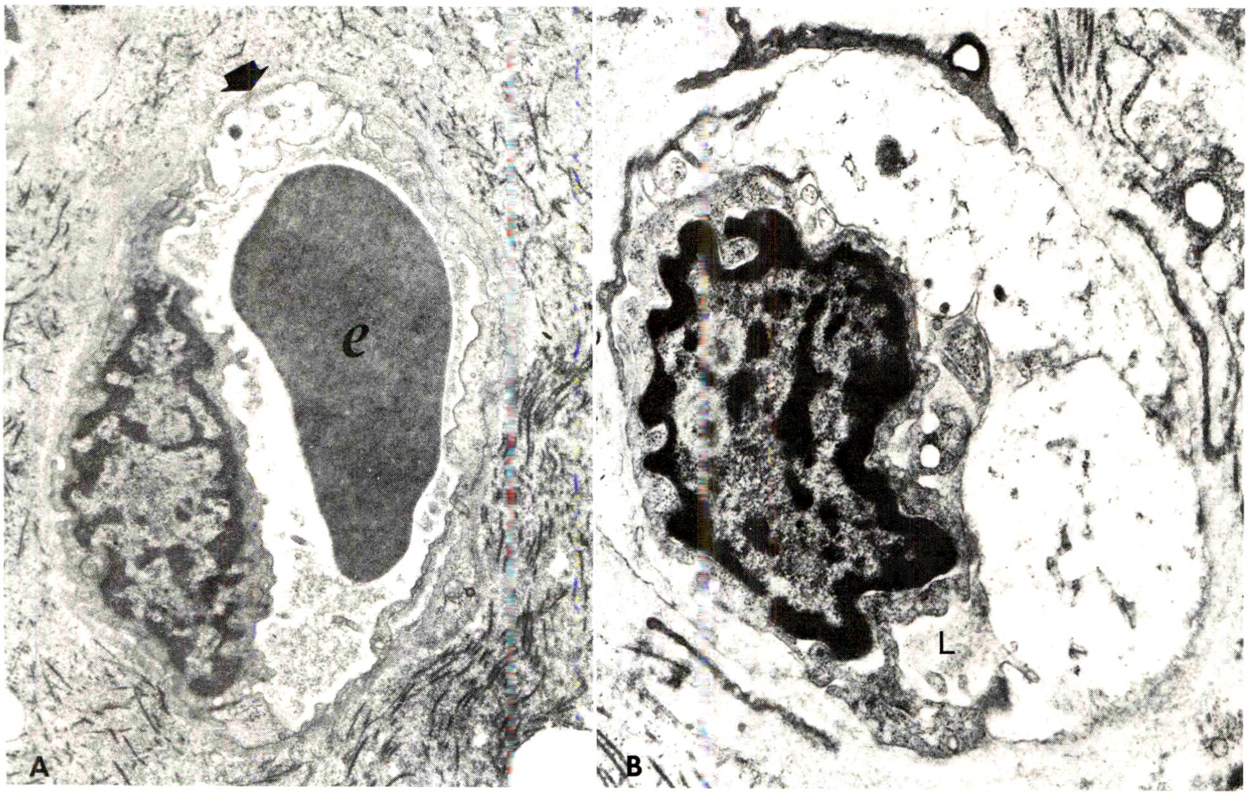

Fig. 2. A) Focal zone of cytoplasmic lucency (arrow) observed at two minutes after provocation. e - Erythrocyte. (x15,000). B) Greatly swollen endothelial cell observed at two minutes after provocation. Luminal space (L) was reduced and contained little plasma. L - Lumen of capillary. (x17,000)

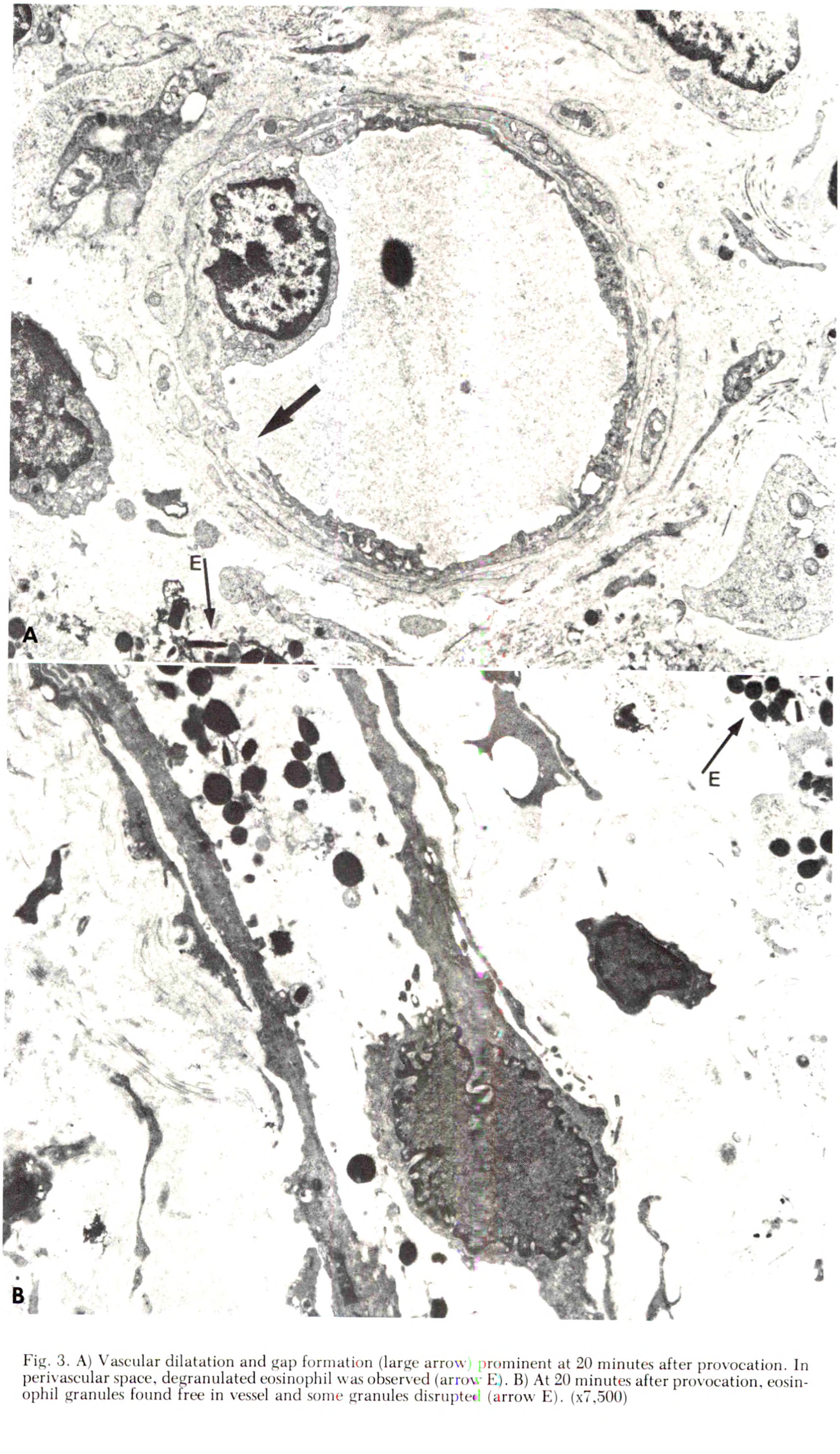

Fig. 3. A) Vascular dilatation and gap formation (large arrow) prominent at 20 minutes after provocation. In perivascular space, degranulated eosinophil was observed (arrow E). B) At 20 minutes after provocation, eosinophil granules found free in vessel and some granules disrupted (arrow E). (x7,500)

the vascular space and contacted eosinophils in the vessel.[6]

DISCUSSION

It is known that allergen-IgE antibody reaction mediates the release of histamine and other chemical mediators from mast cells.[7] Histamine increases the permeability of blood vessels. According to Majno and his colleagues,[8-10] histamine causes the endothelial cells of venules to contract. The result of endothelial contraction is not narrowing of the lumen but a limited separation of the endothelial cells due to high intravascular pressure. Differentiation between capillary and venule is very difficult, especially in nasal mucosa. In capillaries the pericytes are small, few and usually cover a small part of the outer endothelial surface. In venules they are more numerous and extensive, occasionally forming two to three layers.[11] From this point of view, the vessels shown in Figures 1 and 3A,B may represent transitional vessels. Endothelial contraction may cause the marked crowding of erythrocytes; if so, erythrocytes may be forced out through the gaps. Extravasation of erythrocytes through endothelial gaps subsequently may cause filling of these gaps and prevent the allergen from penetrating the vessel. The capillary endothelial gaps are also observed in normal nasal mucosa.[1,2] Although the number of gaps are fewer than found in allergic mucosa, vascular permeability is very high in normal mucosa. However, edema is not observed. It was speculated that since the interstitium surrounding the vessels is loose in normal nasal mucosa, the extravascular fluid passes freely through the interstitium without barrier and is absorbed by other vessels and lymphatics. In allergic mucosa, congestion in the early stage after provocation may inhibit reabsorption of the extravasated fluid, leading to edema. Twenty minutes after provocation, the congestion diminished but the edema persisted. It is speculated that the reason for this is that increased blood flow results in higher intravascular pressure and continued plasma leakage.

In the late stage after provocation, both free and disrupted eosinophil granules were found in the interstitium and intravascularly. Lysosomal enzymes in eosinophil granules may have leaked into the interstitium and intravascular spaces.[6] Wasi et al[12] have shown that lysosomal proteases may release polypeptides capable of causing vascular leakage. Therefore eosinophilic lysosomal enzymes, in addition to histamine from mast cells, were responsible for increased vascular permeability.

Swollen endothelial cells were observed in the early stage after provocation, but it is unknown whether this alteration is stage-specific. Biopsies were obtained during the pollen season; therefore the nasal mucosa had been exposed to pollen before experimental provocation. Swollen endothelial cells were not observed in all cases, but this alteration cannot be attributed to artifact. No evidence of this alteration was observed in control biopsies. Jahnke[4] reported swollen endothelial cells in nasal allergy. Dvorak et al[13] also reported that swollen endothelial cells were observed in delayed-type allergy. Swollen endothelial cells have also been described in states of nonspecific injury to endothelium such as in ischemia[14] and turpentine-induced pleurisy.[15] Therefore, although the swollen microvascular changes we have described are characteristic findings in the evolution of nasal allergic reactions in man, they are not specific for this type of immunologic response. The pathogenesis of endothelial cell injury has not been determined, but it is likely that the allergen directly affects the vessel walls. Endothelial cells beneath the exfoliated epithelial cells are apparently more easily penetrated by the allergen. Swollen endothelial cells are more commonly found in this location.

ACKNOWLEDGMENT — The authors wish to express their thanks to Professor V. Mizuhira for his helpful suggestions and advice.

REFERENCES

1. Watanabe K, Saito Y, Watanabe I, Mizuhira V. Characteristics of capillary permeability in nasal mucosa. Ann Otol Rhinol Laryngol 1980; 89:377-82.
2. Watanabe K, Watanabe I. The ultrastructural characteristics of the capillary walls in human nasal mucosa. Rhinology 1980; 18:183-95.
3. Jackson T, Burson J. Effect of inflammatory mediators on nasal mucosa. Arch Otolaryngol 1977; 103:441-4.
4. Jahnke V. Ultrastruktur der allergischen Nasenschleimhaut des Menschen. Z Laryngol Rhinol 1972; 51:152-62.
5. Toppozada HH, Tallat MA. Tunica propria in chronic allergic rhinitis. Electron microscopic study: II. Nasal blood vessels. ORL 1976; 38:86-92.
6. Watanabe K, Hasegawa M, Saito Y, Takayama S. Eosinophilic leucocytes in nasal allergy — movement of enzymes. Clin Allergy 1977; 7:263-71.
7. Ishizaka K, Ishizaka T. Mechanisms of reaginic hypersensitivity: review. Clin Allergy 1971; 1:9-24.
8. Majno G, Palade GE. Studies on inflammation. I. The effect of histamine and serotonin on vascular permeability: an electron microscopic study. J Biophys Biochem Cytol 1961; 11:571-605.
9. Majno G, Palade GE, Schoefl GI. Studies on inflammation. II. The site of action of histamine and serotonin along the vascular tree: a topographic study. J Biophys Biochem Cytol 1961; 11:607-26.
10. Majno G, Leventhal M. Pathogenesis of histamine-type vascular leakage. Lancet 1967; 8:99-100.
11. Cotran RS, Gattuta ML, Majno G. Studies on inflammation: fate of intramural vascular deposits induced by histamine. Am J Pathol 1965; 47:1045-77.

12. Wasi S, Murray RK, Macmorine DRL, Movat HZ. The role of PMN-leucocyte lysosomes in tissue injury, inflammation and hypersensitivity. II. Studies on the proteolytic activity of PMN leucocyte lysosomes of the rabbit. Br J Exp Pathol 1966; 47:411-23.

13. Dvorak AM, Mihm MC Jr, Dvorak HF. Morphology of delayed-type hypersensitivity reactions in man. II. Ultrastructural alterations affecting the microvasculature and the tissue mast cells. Lab Invest 1976; 34:179-91.

14. Willms-Kretschmer K, Majno G. Ischemia of the skin: electron microscopic study of vascular injury. Am J Pathol 1969; 54:327-53.

15. Ham KN, Hurley JV. Acute inflammation: an electron microscope study of turpentine induced pleurisy in the rat. J Pathol Bacteriol 1965; 90:365-77.

AMERICAN RADIUM SOCIETY

The 65th annual meeting of the American Radium Society will be held April 5-9, 1983, at the Hyatt Regency Hotel in Savannah, Georgia. For further information contact Mrs. Sally Polek, Office of the Secretariat, American Radium Society, 925 Chestnut Street, Philadelphia, PA 19107; (215) 574-3179.

AMERICAN CLEFT PALATE ASSOCIATION/AMERICAN CLEFT PALATE EDUCATIONAL FOUNDATION

The ACPA/ACPEF annual convention will be held May 4-7, 1983, at the Hyatt Regency in Indianapolis, Indiana. For further information contact Jane Angelone Graminski, Administrative Secretary, American Cleft Palate Association, American Cleft Palate Educational Foundation, 331 Salk Hall, University of Pittsburgh, Pittsburgh, PA 15261; (412) 681-9620.

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COMPARISON OF SUBJECTIVE AND RADIOLOGICAL FINDINGS DURING THE COURSE OF ACUTE MAXILLARY SINUSITIS

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Some of the most common symptoms and signs of acute maxillary sinusitis were graded and compared with the radiological findings during the course of the disease. Four different treatment modes were used in 176 patients. The radiological and the subjective findings did not differ among the groups, which consequently were evaluated as an entity. The radiographic results demonstrated that the healing course during the first 15 treatment days follows an even regression line. The subjective findings show a more marked improvement during the first five days than subsequently, and also a more rapid initial improvement than radiography shows. The cough symptom showed the slowest recovery subjectively and also compared most closely with radiological findings. Patients with sinusitis which did not show an initial healing radiographically also had more marked symptoms the fifth day, and vice versa: patients who showed less than average healing subjectively also showed a slower healing radiographically.

INTRODUCTION

It is of interest in any infectious disease to compare the patients' subjective evaluations of their conditions with some kinds of objective measurements. We have previously analyzed the initial symptoms and signs in acute maxillary sinusitis in relation to radiological findings.[1] We found ten symptoms and signs in which there were statistically significant differences between patients without sinusitis, patients with moderate sinusitis, and patients with pronounced sinusitis as measured radiographically at the first medical visit. These were 1) an upper respiratory infection preceding the complaints; 2) nasal discharge; 3) nasal discharge of thick, yellowish or purulent character, 4) general malaise, 5) cough or bronchitis, 6) hyposmia, 7) pains at mastication, 8) fever exceeding 38°C, 9) mucous membrane thickening with mucopurulent or purulent secretion on rhinoscopy, and 10) speech indicating "fullness of the sinuses."

In the present investigation we compared these symptoms and signs with healing shown radiographically during the disease course. As stated in the previous investigation there is very little information concerning specific analyses of symptoms in acute sinusitis. Also, there appears to be an almost complete lack of examinations comparing symptoms with radiographic measurements.

MATERIAL AND METHODS

Patients with clinically suspected acute sinusitis were referred for radiographic examination; a previously developed point scale for the changes was again adopted (Table 1).

The present material includes 176 patients showing mucous membrane thickening and secretion on maxillary sinus radiography (4-6 points). In some cases the frontal sinuses were affected as well, and these patients were also included. Statistical analysis did not show any difference between the subjective evaluation of patients with acute maxillary sinusitis when compared to patients with both acute maxillary and frontal sinusitis. Likewise, some patients showed unilateral and others bilateral maxillary sinusitis. Subjective evaluations of healing did not differ between those two groups and consequently both were included.

The patients were interviewed with regard to the previously mentioned first eight symptoms with the exception of "an upper respiratory infection preceding the complaints." Instead the symptom "pain" was included. The findings on rhinoscopy and the sound of the patient's speech were evaluated by the physician. The symptoms and signs were graded according to the following point scale for complaints: 0 = none, 1 = little, 2 = moderate, and 3 = pronounced; for fever $0 = <37^\circ$C, $1 = 37\text{-}37.9^\circ$C, $2 = 38\text{-}38.9^\circ$C, and $3 = \geq 39^\circ$C.

The patients were randomly allocated into four different treatment groups: amoxicillin, azidocillin, phenylpropanolamine, and pivampicillin. The treatment result is presented elsewhere.[2] Generally the treatment groups showed similar healing according to the symptoms and signs, and consequently the material is treated as an entity. The patients were observed on days 5, 10, and 15 or as close to these days as possible, and were on each visit again analyzed with regard to the symptoms and signs as well as radiographically examined. Patients who demonstrated complete healing radiographically on any of the revisits were included in the material on the subsequent control days as if they were still completely healed; however, radiographic examination was omitted. All data were computer-analyzed using analysis of variance and ± test. A p .05 level was selected for statistical significance.

RESULTS

A comparison between the frequency of the most common sinusitis symptoms in the previous and in

TABLE 1. POINT SCALE FOR RADIOGRAPHIC CHANGES

	Points
No changes	0
Mucous membrane thickening ≤ 6 mm	1
Mucous membrane thickening >6 mm	2
Secretion	2
Mucous membrane thickening ≤ 6 mm + secretion	3
Mucous membrane thickening >6 mm + secretion	4
Complete opacity	6

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TABLE 2. COMPARISON OF FREQUENCY OF SYMPTOMS IN THE PREVIOUS AND PRESENT INVESTIGATIONS

Symptoms	*Previous Investigation* (%)	*Present Investigation* (%)
General malaise	60	92
Fever	28	53
Nasal discharge	97	93
Purulent nasal discharge	75	81
Hyposmia	75	80
Pain	79	83
Mastication pains	30	41
Cough	75	68
Pus on rhinoscopy	50	64
Speech indicating fullness of sinuses	25	65

the present investigation is shown in Table 2. Seven of the ten symptoms have approximately the same occurrence in both investigations. Three symptoms, however, differed; general malaise, fever, and the sound of fullness in the sinuses.

Adopting the 3-point scale for subjective symptoms and for signs, the analyzed variables show a fairly large variation (Fig. 1). Five symptoms on an average had a scale value around 2 points (moderate complaints), three other symptoms, 1.25-1.5 points, and the symptoms fever and mastication pains less than 1 point (small complaints). The comparison between the radiological findings and the subjective findings is presented in Figure 2. Adopting the above point scale, the radiological findings can be illustrated with a fairly even regression line. In contrast the subjective findings show a more pronounced improvement during the first five days of treatment than the radiological findings. After these five days the subjective findings are considerably slower than for the first five days and are also slower than for radiological findings. The symptoms of pain and purulent nasal discharge showed the relatively most subjective "remission" during the 15 observation days with the most pronounced subjective improvement occurring during the first five treatment days. Subjectively, cough showed the slowest initial change as well as the least subjective improvement of all symptoms during the 15 days of observation. In general, very mild symptoms and signs remained after the first five treatment days.

In 101 patients (two patients excluded due to missing information concerning symptoms and signs) the sinuses showed improvement radiographically on the fifth day after treatment started. In 73 patients there was no improvement shown radiographically on the fifth day. The average number of symptoms and signs showing no improvement or deterioration in these patients was 0.81 in the radiographically improved group and 1.7 in the radiographically unimproved group (including 11 radiographically deteriorated patients). These differences are statistically highly significant (p .001).

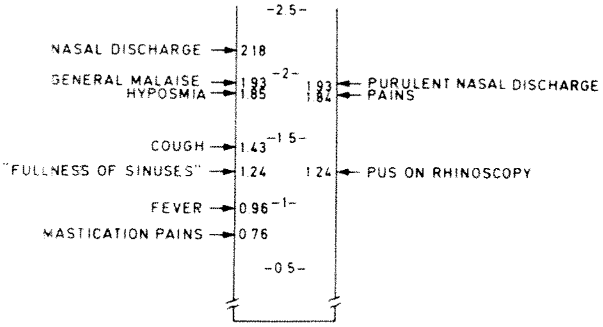

Fig. 1. Initial grading of symptoms and signs in acute maxillary sinusitis.

DISCUSSION

In general, the frequency of symptoms and signs in the present and previous investigations was quite similar. Three symptoms, however, differ: general malaise, fever, and speech indicating fullness of the sinuses. In the present investigation the selection of patients was more careful compared to the previous investigation, ie, only patients with quite substantial symptoms were included. Possibly this explains the high frequency of general malaise, fever, and speech indicating fullness of the sinuses. As for the other symptoms and signs both investigations were quite similar.

Analyzing the initial presence of various symptoms and signs (Fig. 1) it can be seen that the variables form two more or less different groups, one with findings graded >1.8, and another with findings graded <1.5. The average patient shows moderate complaints of nasal discharge, general malaise, hyposmia, pains, purulent discharge on rhinoscopy, and small complaints of the five remaining variables. It is interesting to note again that some of these most marked sinusitis symptoms are quite unspecific and also occur frequently in uncomplicated infectious rhinitis, as well as in vasomotor and allergic rhinitis.

Essentially irrespective of treatment the average patient showed a rapid subjective improvement, and was relieved of the most pronounced sinusitis symptoms during the first five days.

In any infectious disease such as acute maxillary sinusitis with a spontaneous recovery period of a fairly limited time, it is of interest to know if clinical symptoms and signs correlate with other subjective measurements of the disease course. The present investigation shows that such a correlation exists since both the radiographic and the subjective healing course on an average show that few symptoms and signs remain after 15 days. However, subjective healing is more rapid than radiographic healing from the beginning of treatment to the fifth treatment day. In general after five days few symptoms and signs remain of the acute maxillary sinusitis whereas radiography still shows fairly marked

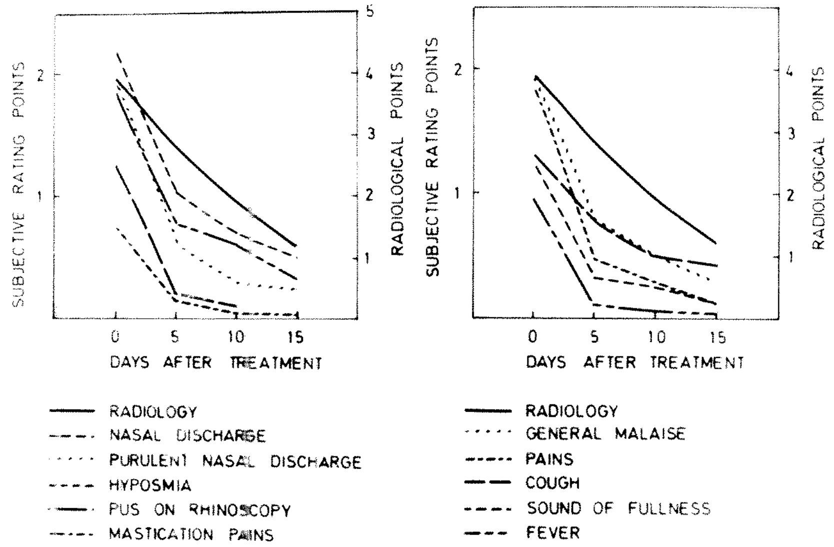

Fig. 2. Relation between radiographic clearing course and symptoms and signs during treatment of acute maxillary sinusitis.

changes. The initial recovery was most rapid for some "dramatic" symptoms and signs; fever, pus on the nasal mucosa on rhinoscopy, mastication pains, and pain. The symptoms which showed the comparatively least improvement during the first five days were cough, nasal discharge, hyposmia, and general malaise. It appears from this that the infectious component of the disease causing fever and purulent nasal discharge, and the sinus ostium occluding component causing the pain, the sound of fullness of the sinuses and mastication pains, are those symptoms which are earliest relieved with antibiotic treatment, while nasal mucous membrane thickening remains somewhat longer, causing rhinal symptoms, ie, nasal discharge, and possibly the sinobronchial symptom, cough. The cough symptom, which shows the least subjective improvement during observed healing, also shows a regression line which is fairly similar to radiographic healing. Obviously, however, the cough symptom could hardly be used as a clinical indication of the healing during the course of sinusitis.

There was an acceptable correlation between radiographic and symptomatological healing, not only in the whole material but also when the material was divided into patients with sinuses shown radiographically to be improved versus sinuses shown radiographically to be unimproved. In the latter group symptoms were also marked. Similarly, when analyzing the number of patients with subjective symptoms which were not improved after five days of treatment, there was a similar significant difference; this group showed less improvement radiographically.

In our previous investigation[1] the literature survey revealed very few specific reports on the frequency of different symptoms in acute maxillary sinusitis. Almost no additional information is available. In sinus disease in children, however, some information is given on the frequency of symptoms.[3,4] We have not been able to find any information concerning the relationship between symptoms and signs on the one hand, and an objective measurement of the sinusitis on the other. The previous and present investigations disclose that the diagnosis of acute maxillary sinusitis based on subjective symptoms and signs is fairly difficult due to the unspecific nature of some of the most marked and frequent symptoms. Consequently, in order to verify the clinical condition some other diagnostic measure is needed. There is good evidence that in the near future we will have new diagnostic measures available which are equally comfortable and less risky for the patients as radiography, eg, ultrasound. At present, however, radiography appears to be the most convenient and rapid diagnostic measure for reflecting the clinical disease course satisfactorily.

REFERENCES

1. Axelsson A, Runze U. Symptoms and signs of acute maxillary sinusitis. ORL 1976; 38:298-308.

2. Axelsson A, Jensen C, Melin O, Singer F, von Sydow C. Treatment of acute maxillary sinusitis. Amoxicillin, azidocillin, phenylpropanolamine, and pivampicillin. Acta Otolaryngol (Stockh) 1981; 91:313-8.

3. Herz G, Gfeller J. Sinusitis in paediatrics. Chemotherapy 1977; 23:50-7.

4. Rachelefsky GS, Goldberg M, Katz RM, et al. Sinus disease in children with respiratory allergy. J Allergy Clin Immunol 1978; 61:310-4.

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MUCOCILIARY FLOW IN THE CANINE FRONTAL SINUS

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The mucociliary flow in the frontal sinus of dogs is in a spiral pattern from medial to lateral. The final evacuation of mucus is through the ostium positioned anteriorly. Mucus flow rate is most rapid in the areas of the ostium and slowest in the area of the intersinus septum. Mucus flow patterns remain the same despite removing the intersinus septum and blocking one frontal sinus ostium. Mucociliary flow rate, however, appears to be diminished in the reoperated frontal sinus. Mucus does not appear to migrate readily across the intersinus septal areas when the septum has been removed and one nasofrontal duct is obstructed.

INTRODUCTION

The first experiments evaluating drainage of the frontal sinus were carried out by Hilding almost 50 years ago.[1] He evaluated the frontal sinus of dogs to determine the character and the migratory patterns of mucus flow within the sinus. In addition, he determined the mucociliary flow rate under normal physiologic conditions. Subsequent studies by Hilding on fresh human cadavers demonstrated frontal sinus mucociliary flow patterns similar to patterns found in the dog.[2] Such findings suggest a high probability that mucus evacuation from the frontal sinus in the canine is similar to that in man. In 1967 Messerklinger evaluated the frontal sinus in human cadavers and confirmed the findings of Hilding.[3] In addition, Messerklinger studied the flow patterns of the frontal sinus in living humans. Ninety-five of 100 frontal sinuses evaluated in living patients demonstrated a consistent spiral flow pattern. The direction of flow was from medial to lateral and from superior to inferior, toward the ostium. Five of 100 patients studied did not conform to this pattern. In these patients mucociliary flow was lateral to medial in one case, directly inferior toward the ostium in another. A third case demonstrated migration of mucus medially to laterally in certain areas and laterally to medially in other areas. No specific flow pattern could be discerned in two patients due to an unusual number of bony septa located within the sinus cavities.[3]

In an attempt to gain an understanding of physiologic alterations that may result from chronic disease, attention has recently focused on the histologic features of the frontal sinus.[4] Hypertrophy of glandular elements in the mucosa of the frontal sinus has been demonstrated in patients with chronic frontal sinusitis. Alterations in the mucociliary flow patterns of the frontal sinus, however, have not been evaluated when the physiology of the frontal sinus is altered by infection or surgery. Whether or not mucociliary flow patterns are altered when obstruction of one of the nasal ducts occurs is unknown. The purpose of this investigation is to establish the normal flow pattern in the canine frontal sinus and to determine whether alterations in physiological conditions within the frontal sinus will result in alteration of mucociliary flow patterns.

METHODS

Six healthy adult dogs were used to evaluate mucociliary flow patterns and flow rates. Through a coronal incision, an oscillating saw was used to elevate an osteoplastic flap and expose the sinus. The intersinus septum was left intact (Fig. 1A). Unlike man, the frontal sinuses of dogs are oriented in a horizontal rather than a vertical plane. The floor of the sinus is consistently at a lower level than the anteriorly situated ostium. All six dogs had similar sized frontal sinuses with anteriorly placed ostia. Each sinus was divided by a single intersinus septum. On each side of the septum a single compartment was observed. A variable number of septa separated shallow recesses posteriorly in each of the frontal sinuses.

A small amount of India ink was placed at various locations on the posterior and anterior walls, as well as on the floor of both frontal sinuses. Observations were made of the mucociliary flow pattern and flow rate for each of the six dogs. Maps of the flow pattern were recorded for each animal.

Once flow patterns and flow rates were established under normal physiologic conditions, two dogs were operated upon and the frontal sinuses exposed by an osteoplastic flap technique similar to the method used in the first group of dogs. The anatomy and flow patterns were observed to be similar to the animals studied previously. The intersinus septum was then removed. A rotating burr was used to lower the intersinus septum until it was level with the floor of the frontal sinus. Care was taken to preserve the normal mucous membrane lining of the remaining frontal sinus. Methyl methacrylate was used to block one of the ostia of the frontal sinus. The osteoplastic bone flap was then replaced and the skin incision closed. Twenty days following surgery, the frontal sinuses were re-explored and mucociliary flow patterns and flow rates were observed.

RESULTS

MUCOCILIARY FLOW PATTERNS AND FLOW RATES IN THE NORMAL FRONTAL SINUS

In each of the dogs examined, the mucociliary flow pattern could be well recognized within one

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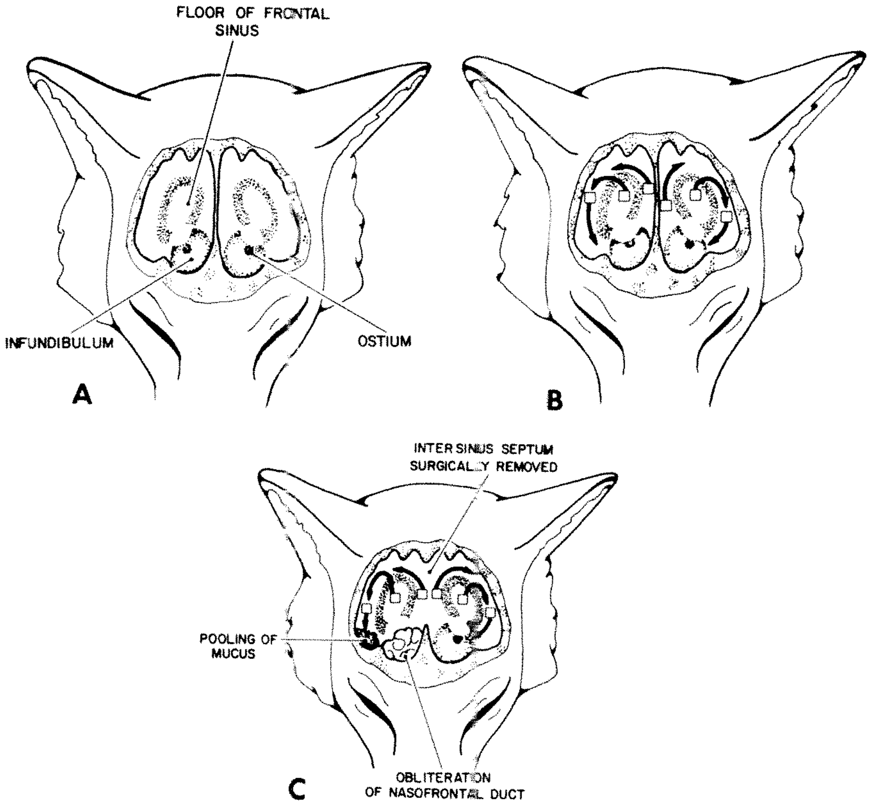
FLOOR OF FRONTAL SINUS
INFUNDIBULUM
OSTIUM
A
B
INTERSINUS SEPTUM SURGICALLY REMOVED
POOLING OF MUCUS
OBLITERATION OF NASOFRONTAL DUCT
C

Fig. 1. A) Surgical exposure of the frontal sinus. Note ostia anteriorly. Frontal sinus in dogs is oriented in a horizontal plane. The floor of the sinus is at a lower level than the ostium. The infundibulum is funnel-shaped forming the entroitus of the nasofrontal duct. B) Normal mucus flow pattern in the canine frontal sinus. Spiral flow pattern (arrows) is demonstrated by utilizing India ink (squares). C) Mucus flow with intersinus septum removed and ostium blocked with methyl methacrylate. Spiral flow remains unchanged. Pooling of mucus occurs in recess of anterior portion of sinus on obstructed side.

hour by observing the movement of the ink under the operating microscope. In each instance, consistent patterns of flow were observed. This pattern was found to be a spiral flow from medial to lateral toward the infundibulum of the nasofrontal duct (Fig. 1B). The table lists the flow patterns and flow rates for different positions within the canine frontal sinus. Flow rates could not be quantitated in millimeters per minute because of the variability in flow rates from animal to animal. Rates were therefore measured in relationship to various regions within a single sinus cavity.

Intersinus Septum. Mucociliary flow on the intersinus septum is directed posteriorly and then laterally. A spiral pattern is observed as mucus flows laterally across the posterior wall. At the same time the flow is directed laterally, it is also directed anteriorly, toward the infundibulum. The mucus flow rate along the intersinus septum is slowest of all areas within the frontal sinus.

MUCOCILIARY FLOW PATTERNS AND COMPARATIVE RATES IN THE CANINE SINUS

Position	*Pattern*	*Rate*
Intersinus septum	Posterolateral (spiral)	+
Anterior wall	Direct to ostium	+ +
Floor	Posterolateral (spiral)	+ + +
Posterior wall	Lateral (spiral)	+ + + +
Lateral wall	Direct to ostium	+ + + + +
Infundibulum	Direct to ostium	+ + + + + +

Anterior Wall. Movement of mucus on the anterior wall is directly anterior and inferior toward the ostium. No lateral migration of mucus is observed. Mucociliary flow rate is similar to flow rates in the area of the intersinus septum.

Floor. Mucociliary flow of the frontal sinus floor is directed posteriorly, then laterally, before emptying into the nasofrontal duct anteriorly. Flow rates of the frontal sinus floor are intermediate compared to the flow rate in the area of the posterior and lateral walls.

Posterior Wall. The floor and posterior wall are continuous in the frontal sinus of dogs. Ink placed in the area of the posterior wall travels toward the lateral wall and then anteriorly toward the ostium, thus forming a spiral flow pattern.

Lateral Wall. Unlike the floor and posterior wall of the frontal sinus, mucus on the lateral wall is carried directly into the ostium without demonstrating any spiral flow pattern. Mucociliary flow rate in the area of the lateral wall is more rapid than any other location within the frontal sinus except for the infundibulum area.

Infundibulum. The infundibulum is defined as that portion of the floor of the frontal sinus that is funnel-shaped forming the entroitus of the nasofrontal duct. In the immediate vicinity of the infundibulum and extending into the ostium, mucociliary flow is directly toward the ostium anteriorly. No spiral flow pattern is observed in the area of the infundiblum. In contrast, mucociliary flow peripheral to the junction of the infundiblum with the remaining floor of the frontal sinus is in a spiral flow pattern toward the lateral wall. Mucus flow rate within the infundibulum is the most rapid of all areas of the frontal sinus.

MUCOCILIARY FLOW PATTERNS AND FLOW RATES IN THE PATHOLOGICALLY ALTERED FRONTAL SINUS

Exploration of the frontal sinuses of the dogs having undergone previous resection of the intersinus septum and obstruction of one of the nasofrontal ducts revealed pooling of the thick clear mucus (Fig. 1C). The pooling was isolated to the lateral wall and floor on the side of the obstructed duct. The condition of the mucosa, however, appeared unchanged from that noted at the first operation, both grossly and under the operating microscope. Mucociliary flow patterns were essentially identical to the pattern of flow observed at the time the intersinus septum was removed. Flow rates in all areas were more sluggish compared to the flow rates in the original unaltered sinus. Flow rates were reduced approximately 25% compared to the flow rates observed at the initial operative procedure. However, specific quantitative differences were not established.

There appeared to be little or no movement of ink in the area of the previously removed intersinus septum. The ink remained stationary in these areas for as long as one-half hour. Little or no movement was observed well beyond the time required for ink deposits in other areas of the sinus to be completely cleared from the sinus.

DISCUSSION

In instances of nasofrontal duct obstruction and subsequent unilateral frontal sinus disease, resection of the intersinus septum has been recommended.[5] The rationale for this approach is prevention of stasis. Mucus on the diseased side of the frontal sinus is presumably transported toward the healthy side and downward through the nasofrontal duct.

Removal of the intersinus septum and obstruction of one of the nasofrontal ducts in dogs did not appear to influence the mucociliary flow pattern. Mucus remained stationary in the area of the resected intersinus septum. The lack of mucociliary flow across the septal area accounted for pooling of mucus on the side of nasofrontal duct obstruction. Although stasis was clearly present on the obstructed side, no evidence of infection was observed. Only 20 days elapsed between the creation of the unilateral nasofrontal duct obstruction and re-exploration of the frontal sinus. Whether mucociliary flow patterns are altered when nasofrontal duct obstruction is present for a longer interval is unknown.

Another unanswered question is whether mucus flow patterns are altered when the mucosa is removed from the frontal sinus and allowed to regenerate. Regenerated mucosa in the maxillary sinus becomes reoriented and demonstrates mucociliary flow toward surgically created antral-meatal windows.[6] The same may be anticipated in the frontal sinus. If reorientation of mucus flow patterns does occur in the frontal sinus, removal of the mucosa on the diseased side may be recommended in addition to removal of the intersinus septum. Such a procedure may eliminate the pooling of mucus and subsequent stasis observed when only the intersinus septum is removed.

REFERENCES

1. Hilding AC. The physiology of drainage of nasal mucus. III. Experimental work on the accessory sinuses. Am J Physiol 1932; 100:664-70.

2. Hilding AC. The physiology of nasal mucus. IV. Drainage of the accessory sinuses in man. Ann Otol Rhinol Laryngol 1944; 53:35-41.

3. Messerklinger W. Ist in allen Mensch lichen stirnhohlen das prinzip des Sekvettransportes gleich? Arch Klin Exp Ohren Nasen Kehlkopheilkd 1967; 189:317-26.

4. Mirko T, Christian M, Zdenek N. Quantitative histologic features of the normal frontal sinus. Arch Otolaryngol 1980; 106:143-8.

5. Goode RL, Strelzow V, Fee WE Jr. Frontal sinus septectomy for chronic unilateral sinusitis. Otolaryngol Head Neck Surg 1980; 88:18-21.

6. Proetz AW. The displacement method of sinus diagnosis and treatment. 2nd ed. St. Louis: Annals Publishing Co, 1939.

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SARCOMAS OF THE LARYNX

REPORT OF TEN CASES

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The clinical and pathologic findings of 10 laryngeal sarcomas (8 fibrosarcomas and 2 rhabdomyosarcomas) are reported. These cases constituted 0.02% of the 4,717 patients with carcinoma histologically verified at Faculty of Medicine in Istanbul from 1934 to 1980. Analysis of laryngeal fibrosarcomas reveals that they are more frequently seen in the fourth and fifth decades, while rhabdomyosarcomas of the larynx are rather tumors of childhood. They are generally less infiltrating than carcinomas and tend to grow as polypoid masses. Metastases are rare but recurrences are frequently seen.

Statistics dealing with a large series of patients with laryngeal cancer indicate that the incidence of sarcoma is less than 1%.[1-3] More than 50% of laryngeal sarcomas are fibrosarcomas of either mature or immature types.[4-6] Next in frequency are chondrosarcomas, osteosarcomas and very rarely leiomyosarcomas and liposarcomas.[1,7-9] Only 12 proven cases of rhabdomyosarcoma of the larynx are reported in the literature.[10-17]

The purpose of this article is to report the clinicopathological observations dealing with a series of 10 laryngeal sarcomas (8 fibrosarcomas and 2 rhabdomyosarcomas) which were found in a survey of 4,717 malignant tumors of the larynx (0.2%) diagnosed histologically at Faculty of Medicine of Istanbul from 1934 to 1980. Lymphomas involving the larynx (six cases) were not included in this series. All available hematoxylin and eosin-stained sections were reviewed in order to establish the unequivocal evidence of the mesenchymatous origin of these lesions. Paraffin-preserved blocks were sectioned and stained with van Gieson, PTAH and silver reticulum stain (Gomori's silver method) whenever indicated. The clinical features that could be found from the records and pathologic findings of these cases are summarized in Tables 1 and 2.

FINDINGS

Fibrosarcomas. Age distribution in the eight cases varied between 8 and 60 years, two patients being 8 and 23 years of age. The mean age of the six other patients was found to be 58.8 years. Three of them were females and five males. Common initial complaints were hoarseness, dyspnea and pain (five patients). The mean duration of these symptoms was nine months.

The tumoral growth in most of these cases resembled a pink polypoid mass with a broad base usually

TABLE 1. CLINICAL DATA AND HISTOLOGIC FINDINGS OF FIBROSARCOMAS OF THE LARYNX

Case No.	*Age (yr)*	*Sex*	*Site*	*Size (cm)*	*Symptoms and Clinical Diagnosis*	*Duration of Symptoms (yr)*	*Histological Differentiation*	*Follow-up*
1	50	F	Larynx	—	Papilloma	1	Poor	Unavailable
2	48	F	Anterior commissure; anterior third of left vocal cord	1	Hoarseness, dyspnea and pain, tumoral mass	$^1/_2$	Good	Unavailable
3	23	M	Arytenoid	—	Pain and hoarseness, ulcerated mass	—	Poor	Unavailable
4	52	M	Laryngeal site of epiglottis	1.5	Tumoral mass	1	Moderate	Unavailable
5	60	M	Epiglottis and oropharynx	1-2	Dysphagia and pain, multiple nodular mass	1	Good	No recurrence, alive and well after 2 yr
6	50	M	Larynx	1 x 0.5	Hoarseness, dyspnea, pain, infiltration of thyroid gland	$^1/_4$	Poor	Unavailable
7	8	M	Left vocal cord	2	Hoarseness and dyspnea, tumoral mass	—	Good	No recurrence, alive and well after 3 yr
8	45	F	Right vocal cord and ventricle	1-2	Hoarseness and dyspnea, tumoral mass	1	Moderate	3 recurrences, alive and well after 3 yr

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TABLE 2. CASES OF EMBRYONAL RHABDOMYOSARCOMA (BOTRYOID PATTERN)

Case No.	*Age (yr)*	*Sex*	*Site*	*Size (cm)*	*Clinical Findings and Diagnosis*	*Duration of Symptoms (yr)*	*Follow-up*
1	9	M	Left vocal cord, ventricular fold and side of pharynx	3	Polypoid masses	1/4	8 recurrences and died of disease after 5 yr
2	13	M	Laryngeal side of epiglottis	2	Pedunculated, soft polypoid mass	1	2 recurrences, living with tumor after 2 yr

covered by epithelium. The majority of the tumors were firm. In one case the tumor had expanded into the thyroid gland (case 6).

The main sites of the tumors were the vocal cord, the ventricular fold, arytenoid and epiglottic areas. None of the patients had clinically positive cervical metastases.

The histopathological pattern of this tumor was similar to fibrosarcoma elsewhere in the body. According to the cellularity, to the amount of interstitial collagenous tissue and to the nuclear atypism and pleomorphism, 3 of the cases were well differentiated (cases 2, 5 and 7), 2 of them were moderately (cases 4 and 8) and 3 others were poorly differentiated (cases 1, 3 and 6) (Figs. 1 and 2).

Due to the retrospective nature of this study the follow-up data of most of the cases were unavailable, except for three cases (5, 7, 8). In the eighth case, the polypoid tumor involving the right vocal cord and ventricular fold showed three recurrences in three years after laryngectomy and radiation. In two others (cases 5 and 7), recurrences following radiotherapy and local surgical intervention were not seen for two and three years.

Rhabdomyosarcomas. The clinical and pathologic findings of two cases of rhabdomyosarcomas originating in the laryngeal area are summarized in Table 2. Both of the patients initially complained of airway encroachment, pain and hoarseness. They were both males, one being 9 and the other 13 years old. The size of the tumors varied from 2 to 3 cm and one of the tumors was pedunculated (case 2). Both of the tumors showed polypoid soft masses protruding into the lumen (botryoid type) and arising from the laryngeal side of the epiglottis in case 2 and left vocal cord and ventricle with involvement of the left side of the pharynx in case 1. In both

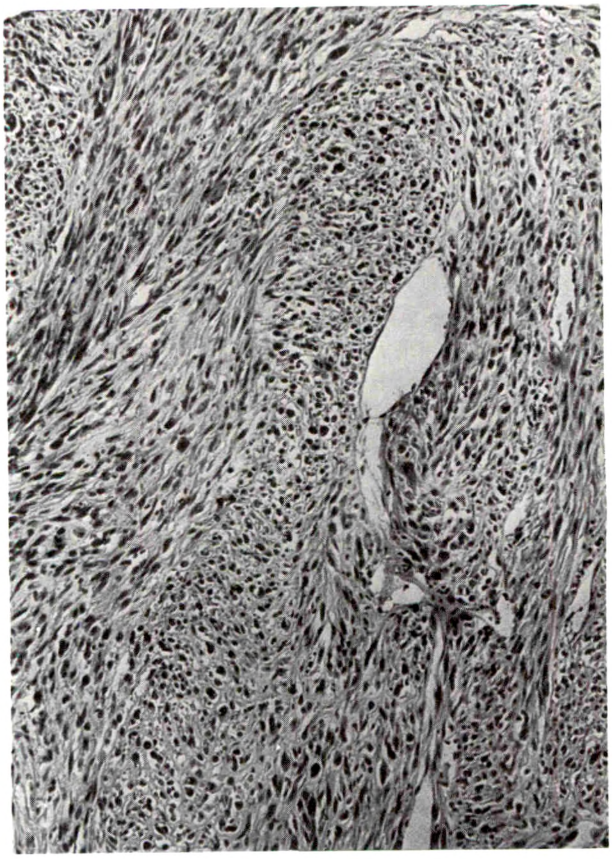

Fig. 1. (Case 4) Fibrosarcoma. Tumor is highly cellular and composed of atypical fibrocytic and fibroblastic elements exhibiting moderate degree of pleomorphism. (H & E, x 125)

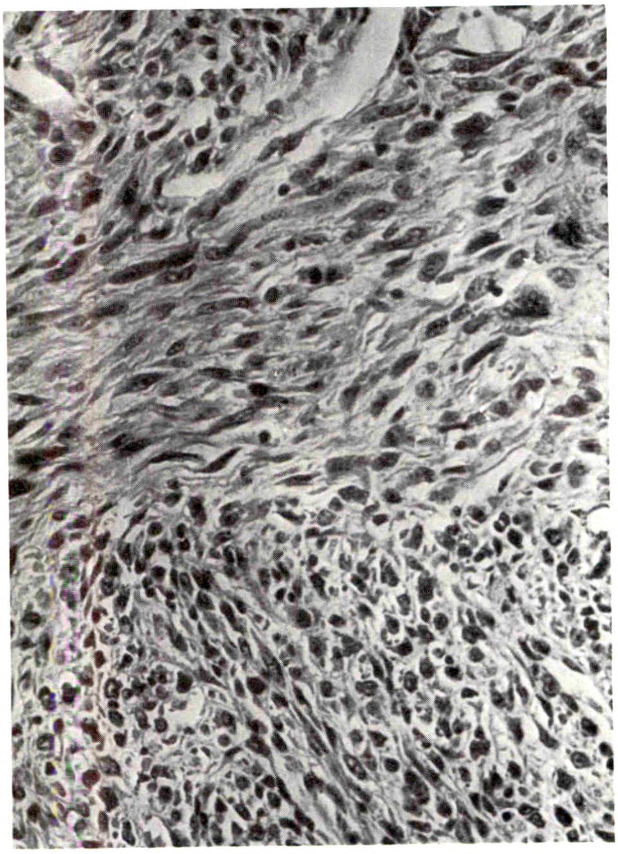

Fig. 2. (Case 8) Fibrosarcoma. Micrograph showing tumor consisting of moderately differentiated spindle cells. (H & E, x 325)

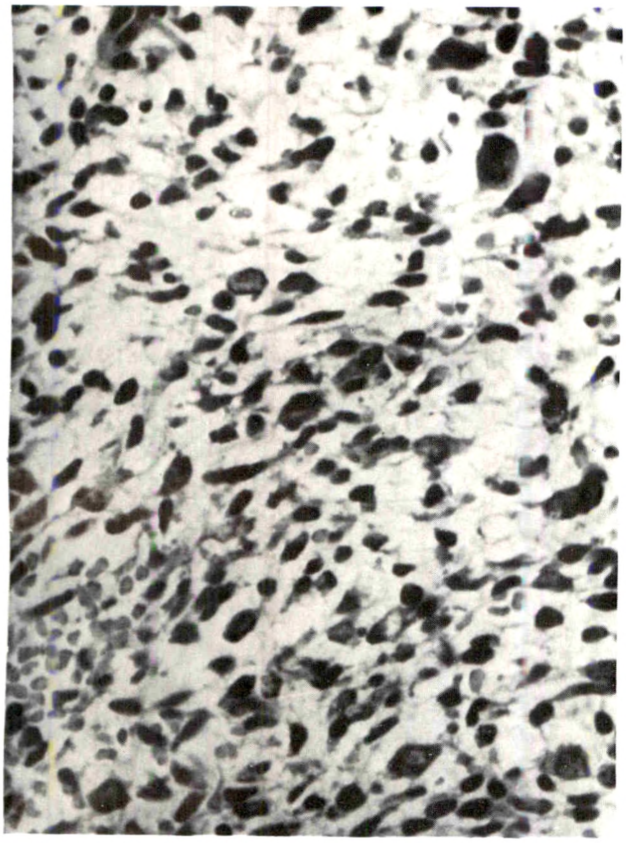

Fig. 3. (Case 2) Botryoid rhabdomyosarcoma. Marked nuclear pleomorphism and occasional giant cells of multiple nuclei. (H & E, x 500)

cases, the patients were treated with radiotherapy and subsequent laryngectomy. The first case showed eight successive recurrences following excisions and radiotherapy in the five years before death, and the tumor expanded to oropharyngeal and nasopharyngeal areas. The surrounding lymph nodes showed no metastases. In the second patient, two recurrences occurred in two years. This patient is alive with tumor and has no palpable cervical and distant metastases.

The tumors were composed of a dense subepithelial aggregate of tumor cells, either rounded or spindle-shaped, forming interlacing bundles. The cells had deeply stained nuclei. Larger and smaller areas of loose myxomatous stroma were scattered, especially in the vicinity of ectatic vessels. A few of the tumor cells had a prominent acidophilic cytoplasm suggesting rhabdomyoblasts which were occasionally grouped together. Occasional giant cells of multiple nuclei were present between individual spindle cells. In none of the cases could definite cross striations be noted (Fig. 3).

COMMENTS

The follow-up data of three of the cases showed that the well-differentiated types (cases 5 and 7) had no recurrences and no metastases, while the moderately differentiated type showed three successive recurrences in three years (case 8).

In spite of the fact that fibrosarcoma is mostly seen in adults in late years of life, Rigby and Holinger[18] described a fibrosarcoma in an infant, and one of the cases presented in this paper was found only in an 8-year-old male (case 7).

The polypoid pattern described in laryngeal rhabdomyosarcomas, as well as in our cases, was similar to that in embryonal rhabdomyosarcomas arising from the genitourinary system and of other anatomical locations.[3,19] Nearly all of these tumors, as it is noted in those tumors of the head and neck, are the tumors of childhood.[20,21] The botryoid pattern seen in these cases should be related to the site of origin and the age of patients.

Although rhabdomyosarcomas are highly malignant neoplasms of striated muscle, the clinical course of rhabdomyosarcoma in the laryngeal area seems to be similar to botryoid tumors of the urogenital system in that metastases infrequently occur but recurrences are the rule. Accordingly, in both of these presented cases, the insidious course and invasive growth of the tumor with recurrences was noted.

REFERENCES

1. Batsakis JG, Fox JE. Supporting tissue neoplasms of the larynx. Surg Gynecol Obstet 1970; 131:989-97.

2. Ferlito A. Histological classification of larynx and hypolarynx cancers and their clinical implications. Acta Otolaryngol (Stockh) 1976; 342:1-88.

3. Mostofi FK, Morse WH. Polypoid rhabdomyosarcoma (sarcoma botryoides) of bladder in children. J Urol 1952; 67:681-7.

4. Friedmann I. Sarcomas of the larynx. Can J Otolaryngol 1975; 4:297-302.

5. Gorenstein A, Neal HB, Weiland LH, Devine KD. Sarcomas of the larynx. Arch Otolaryngol 1980; 106:8-12.

6. Krajina Z. Laryngeal sarcoma. Can J Otolaryngol 1975; 4:303-6.

7. Huizenga CH, Balogh K. Cartilaginous tumors of the larynx: a clinicopathologic study of 10 new cases and a review of the literature. Cancer 1970; 26:201-10.

8. Kawabe Y, Kondo T. Laryngeal leiomyosarcoma. Otolaryngology (Tokyo) 1967; 39:427-32.

9. Velek JP. Liposarcoma of the larynx. Trans Am Acad Ophthalmol Otolaryngol 1976; 82:569-70.

10. Batsakis JG, Fox JE. Rhabdomyosarcoma of the larynx. Report of a case. Arch Otolaryngol 1970; 91:136-40.

11. Canalis RF, Plats CE, Cohn AM. Laryngeal rhabdomyosarcoma. Arch Otolaryngol 1976; 102:104-7.

12. Frugoni P, Ferlito A. Pleomorphic rhabdomyosarcoma of the larynx. A case report and review of the literature. J Laryngol Otol 1976; 90:687-98.

13. Glick HA. An unusual neoplasm in the larynx of a child.

Rhabdomyosarcoma. Ann Otol Rhinol Laryngol 1944; 53: 699-704.

14. Hall-Jones J. Rhabdomyosarcoma of the larynx. J Laryngol Otol 1975; 89:969-76.

15. Harris HH. Rhabdomyosarcoma of the larynx: report of a case. Arch Otolaryngol 1961; 74:205-9.

16. Muhtar H, Karaca AR, Gür H. Bir larenks rhabdomyosarcoma vakasi. Acta Oncol Turcica 1970; 3:159-64.

17. Rodriguez LA, Ziskind J. Rhabdomyosarcoma of the larynx. Laryngoscope 1970; 80:1733-9.

18. Rigby RC, Holinger P. Fibrosarcoma of the larynx in an infant. Arch Otolaryngol 1943; 37:425-9.

19. Farinacci CJ, Fairchild JP, Sulak MH, Gilpatrick CW. Sarcoma botryoides (a form of embryonal rhabdomyosarcoma of the common bile duct). Cancer 1956; 9:408-17.

20. Dito WR, Batsakis JG. Rhabdomyosarcoma of the head and neck. Arch Surg 1962; 84:582-8.

21. Stobbe GD, Dargeon HW. Embryonal rhabdomyosarcoma of the head and neck in children and adolescents. Cancer 1950; 3:826-36.

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THIRD INTERNATIONAL SYMPOSIUM ON RECENT ADVANCES IN OTITIS MEDIA WITH EFFUSION

The Third International Symposium on Recent Advances in Otitis Media with Effusion, sponsored by the Ohio State University College of Medicine, will be held on May 17-20, 1983, at the Bahia Mar Hotel in Fort Lauderdale, Florida. The purpose of the symposium is to update information and gain important new concepts on otitis media with effusion, or serous (secretory) otitis media.

Topics included are: definition, classification, epidemiology, etiology, pathogenesis, pathology, microbiology, immunology, diagnosis, mass screening, medical and surgical management, prevention, and outcome. Over 80 outstanding speakers and panelists from the United States and abroad are included.

Registration is $250 (residents $180). This continuing medical education offering will meet the criteria for Category I approval of the Physician's Recognition Award of the AMA. To receive further information, write David J. Lim, MD, 4331 University Hospitals Clinic, 456 Clinic Drive, Columbus, OH 43210.

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INTERNATIONAL ELECTRIC RESPONSE AUDIOMETRY STUDY GROUP

The International Electric Response Audiometry Study Group will hold its eighth biennial meeting at the University of Ottawa on July 4-8, 1983. The meeting will consist of invited review lectures, symposia, platform presentations and poster displays in all areas of auditory evoked potential research. The deadline for receipt of abstracts is March 15th, 1983. For more information contact Dr. T. W. Picton, Division of Neurology, Ottawa General Hospital, 501 Smyth Road, Ottawa, Canada, K1H 8L6.

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VOCAL FOLD PARESIS IN SHY-DRAGER SYNDROME

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Twelve patients with Shy-Drager syndrome (SDS) presenting symptoms of multiple nervous system atrophy and orthostatic hypotension were examined for laryngeal movement disorders and vocal impairment in speech. Vocal fold abductor paresis was found in 11 patients and was bilateral in 10. Speech task performance was recorded in SDS patients, Parkinson patients and age- and sex-matched controls. Trained listeners with inter-rated reliability≥ .85 judged each recording on 20 attributes while blind to speaker identity. SDS patients had a breathy and strained voice quality, reduced loudness, monopitch and monoloudness, imprecise consonants, variations in rate and rate-slowing, suggesting a flaccid type of dysarthria. In comparison with Parkinson patients, SDS patients had excess vocal hoarseness, intermittent glottal fry and a slow and deliberate speaking rate. Orthostatic hypotension, laryngeal stridor, hoarseness, intermittent glottal fry and slow speech rate were found to be discriminating symptoms of SDS.

INTRODUCTION

The study of laryngeal function abnormalities in patients with central nervous system pathology and laryngeal dysfunction may be valuable for improved understanding of the neural control of normal laryngeal function. The Shy-Drager syndrome (SDS),[1] one form of neurogenic orthostatic hypotension, usually presents in late middle age with a gradual onset of failure of the autonomic nervous system and signs of multiple systems atrophy[2] affecting corticospinal and cerebellar pathways as well as the basal ganglia. Initial symptoms include postural hypotension, impotence, sphincter dysfunction, and anhydrosis with later progression to panautonomic failure. The autonomic symptoms are usually followed by atypical parkinsonism and/or cerebellar dysfunction with eventual progression to devastating debilitation and death. Respiratory failure requiring tracheostomy has been reported in SDS[3] and prompted us to further evaluate laryngeal and speech functions in a series of patients presenting with this syndrome.

SDS has some similarities to Parkinson disease. The latter is confined to the nigrostriatal neuronal system while SDS is a multiple system disorder involving the nigrostriatal, olivoponto cerebellar, brainstem and intermediolateral column of the spinal cord.[4,5] Using surface electromyography of the intrinsic laryngeal musculature, Guidi et al[6] found denervation of the posterior cricoarytenoid in five patients with SDS and interarytenoid abnormalities in three cases. By comparison, only one third of patients with idiopathic parkinsonism presented minor electromyographic abnormalities. Since both syndromes present phonatory disorders, the differences in laryngeal and speech dysfunctions between the two disorders was of interest to determine the effects of pathology involving different components of the CNS on vocal function.

METHODS

Twelve consecutive patients who met the criteria for diagnosis of SDS with orthostatic hypotension and multiple CNS defects[1] were included in the investigation. All had normal glucose tolerance and no evidence of amyloidosis or any disorder known to be associated with orthostatic hypotension.

Clinical Evaluation. The patients and their families were questioned about upper respiratory tract difficulties, changes in voice, snoring, respiratory stridor, and episodes of apnea. Each patient's larynx and pharynx were examined by one observer on multiple occasions. Laryngeal and vocal fold movement was observed by indirect laryngoscopy during quiet respiration, deep inspiration and expiration, and phonation. A fiberoptic nasolaryngoscope was used when indirect laryngoscopy was not feasible and to visualize the larynx during connected speech. In patients with marked abductor paresis, prolonged observation was necessary to determine whether there was adductor motion of the arytenoids.

Speech Analyses. The last seven SDS patients were included in a study of phonatory function. Each subject's speech was recorded in a sound-treated environment while seated in the upright position in a high-backed chair with arm rests. All subjects tolerated the sitting position well for 15 minutes of speech recording. Recordings were made with a head-held Electret condensor microphone with a constant mouth-to-microphone distance of 7.5 cm. Scotch low noise magnetic recording tape No. 206 was used with a full tract Nagra No. 4-S stereo portable tape recorder at 7 ½ ips. Before each recording, a 1000-Hz calibration tone was played at 85 dB SPL and the sound level read at the face of the subject's microphone with a General Radio sound level meter model No. 1933. An instruction tape provided the speech items for imitation including extended vowel phonation, sentence imitation, rapid repetition of vowels and consonant-vowel syllables, rapid onset of phonation, pitch and intensity imitations and stress contrasts on polysyllabic words.

Age- and sex-matched normal controls without a history or symptoms of neurologic, otolaryngologic or speech and language disorders were recorded in the same manner as the SDS patients. Similarly, seven age- and sex-matched patients with idiopathic parkinsonism were selected for study. All Parkinson patients were receiving L-Dopa therapy (4-7 mg daily), had tremor and rigidity

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TABLE 1. MEAN AND STANDARD DEVIATIONS OF MODE RATINGS DIFFERING BETWEEN SHY-DRAGER PATIENTS AND AGE- AND SEX-MATCHED NORMAL CONTROLS

	Shy-Drager Patients		*Normal Controls*			
Speech Attribute	$\bar{X}$	*SD*	$\bar{X}$	*SD*	*F value**	*p of F*
Strain strangle	3.43	1.62	1.71	0.76	5.63	.050
Breathy	3.29	2.29	1.57	0.79	6.08	.040
Imprecise consonants	4.00	1.92	1.57	0.54	16.33	.006
Variable rate	4.86	1.07	2.86	1.46	6.06	.040
Monopitch	4.00	1.63	1.86	0.69	14.41	.009
Monoloudness	3.86	1.46	2.57	0.98	5.37	.050
Reduced stress	3.43	1.62	1.71	1.11	6.95	.030
Intensity	4.71	2.43	7.86	2.55	5.81	.050
Rate	4.86	1.46	7.29	0.95	12.76	.010

*ANOVA 1-way for repeated measures on log-transformed data.

and were without signs of dyskinesia when recorded. All were ambulatory for short distances, had bilateral movement problems and speech symptoms.

Three speech pathology graduate students were trained to rate tape recordings of patients' speech on 20 different attributes (see appendix). The speech attributes selected for training were those identified by Darley et al[7] as characteristic of hypokinetic and flaccid dysarthrias.

Rating scales from 1 to 7 were used for each of the 17 attributes with 1 representing no occurrence of abnormality and 7 representing complete dysfunction. Pitch level, intensity level and overall rate were judged on a 13-point scale with a normal rating being a 7; 6 through 1 being progressively too low, too soft or too slow; and 8 through 13 being progressively too high, too loud or too fast.

Rater listening training was extensive; 20 1-hour sessions of listening to training tapes of dysarthric and normal speakers were required to reach a criterion intraclass correlation coefficient value of 0.85 or greater on each of the attribute rating scales prior to rating the experimental tapes.

The 21 tapes of SDS, control and parkinson patients were played to the three judges following training with no information provided regarding speaker identity. Listeners were 60 cm from a Sony TC-105 tape recorder in a sound-controlled room. During playback, the calibration tone was adjusted to read the same SPL on a sound level meter at the listener's ears as was measured at the subject's microphone during recording. The listeners rated each tape on all 20 attributes; the mode rating for each subject for each attribute was selected for analysis. To provide a common reference for judging pitch and intensity, synthesized /a/ vowels with fundamental frequencies of 100 Hz and 200 Hz for males and females respectively were played at 80 dB SPL re 0.0002 dynes/cm^2 prior to each subject recording.

RESULTS

Clinical Findings. The neurological symptoms of the group of patients recorded for this study were previously described by Williams et al.[3] The patients ranged in age from 54 to 68 years, with a duration of disease from 2 to 8 years. All of the SDS patients had parkinsonian symptoms ranging from mild to severe. Nine of the 12 patients in the series had cerebellar signs, none severe. Eleven of the 12 had some bulbar dysfunction, and all had sexual and sphincter dysfunction and significant postural hypotension.

The respiratory symptoms in these patients typically began with increased snoring at night. This was a complaint in 9 of the 12 patients, and was predictive of eventual progression to stridor (in 7 of the 9 patients) and respiratory failure (in 6 of the 9 patients). Symptoms were often worse at night, and sleep apnea was a major problem in 2 of the 12 patients. Hoarseness was a complaint of only two patients and did not correlate with the degree of vocal fold paresis.

On initial examination of the larynx, 11 of the 12 patients demonstrated abductor paresis of the vocal folds. Two of these 11 patients had unilateral paresis when first examined but over time they both progressed to bilateral abductor paresis. The longest follow-up was for three years and one patient did not develop paresis during this time.

The typical pattern observed was a progressive inability to abduct the vocal folds in deep respiration. Thus, the resting and inspiratory positions of the folds remained the same. Over time the glottic opening typically became progressively narrower at maximum inspiration. Adductor motion was definitely present in early stages but necessarily became more difficult to assess as the resting position of the vocal folds approached the midline. Voice tapes were obtained when the patients were initially examined and clinical impressions of vocal pathology corresponded with overall syndrome severity rather than abductor paresis. Six of the 12 patients eventually required tracheostomy for chronic respiratory failure.

The more severely affected patients had marked weakness of the accessory respiratory musculature. Only one patient developed respiratory obstruction prior to exhibiting parkinsonian symptoms. Another patient had a glottic chink of only 2 mm but tolerated the glottic obstruction well due to no significant weakness of the accessory respiratory musculature. Limited movement of the soft palate and swallowing difficulty was noted in some cases.

The patients who required tracheostomy were relieved of their respiratory failure and sleep apnea. A permanent skin-flap-lined stoma was used and was plugged during the day, or a Tucker valve tube was used to allow the patient to speak. This was prefer-

TABLE 2. MEAN AND STANDARD DEVIATIONS OF MODE RATINGS OF SHY-DRAGER AND AGE- AND SEX-MATCHED PARKINSON PATIENTS

	Shy-Drager Patients		*Parkinson Patients*			
Speech Attribute	$\bar{X}$	*SD*	$\bar{X}$	*SD*	*F value**	*p of F*
Wet hoarseness	2.86	1.35	1.86	1.57	7.18	.03
Glottal fry	2.29	0.76	1.43	0.54	9.85	.02
Excess stress	1.71	0.76	1.00	0.00	7.18	.03
Rate	4.86	1.46	7.86	2.27	15.21	.007

able to surgical abduction of the vocal cord, since these patients could communicate only by speech given their other neuromotor impairments associated with SDS.

Speech Findings. The intraclass correlation coefficients, a measure of inter-rater reliability in judging the experimental tape recordings, are included in the appendix for each speech attribute. These were equal to or greater than 0.85 for every attribute except increasing rate which was therefore omitted from further consideration.

The mean mode ratings for each group on the 19 remaining attributes were submitted to two analyses of variance for each attribute: first, to compare the SDS patients with their age- and sex-matched controls; and second, to compare the SDS patients with age- and sex-matched hypokinetic parkinsonian patients.

The SDS patients differed significantly ($p < .05$) from the normal controls on 9 of the 19 speech attributes. The means and standard deviations of each group along with the F statistics and their probabilities are presented in Table 1. SDS patients' speech differed from normal controls in the following respects: their vocal quality was breathy, strained or strangled, too soft (low intensity) and reduced in stress with monopitch and monoloudness; they showed significant imprecision of consonants, variations of rate and rate-slowing. These latter characteristics are those of a flaccid dysarthria associated with bulbar disease,[7] and include symptoms of both laryngeal and oral neuromotor impairments.

The SDS patients were also compared with age- and sex-matched parkinsonian patients to determine how their vocal and speech symptoms differed from those of patients with dysfunction primarily of the nigrostriatal neuronal system. The two groups of patients differed significantly on four attributes. The means and standard deviations of each group, along with the F statistics and their probabilities for the four attributes, are presented in Table 2. The SDS patients' ratings on vocal hoarseness and glottal fry (diplophonia) were more severe than the Parkinson patients. Their speaking rate was much slower with greater excessive and equal stress on each syllable than the Parkinson patients.

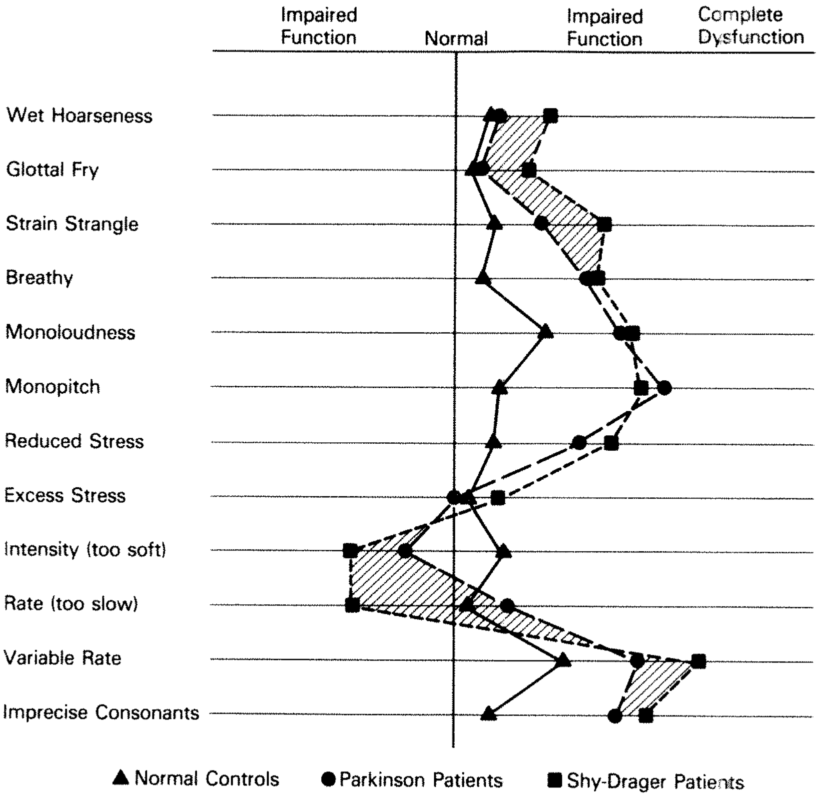
The speech attributes where there were significant differences between the three groups are illustrated in the Figure. Those attributes most impaired in SDS included hoarseness, glottal fry, soft intensity, slow rate, variable rate and imprecise consonants. These symptoms suggest a flaccid type of dysarthria consonant with disease affecting both the nucleus ambiguus and the hypoglossal nucleus in the medulla.

Finally, to determine which speech characteristics differentiate between the three groups, a stepwise discriminant function analysis (Mahal Method) was computed. Maximum separation with eigenvalues of 2.27 and 0.91 and p values of .0001 and .004 was obtained by combining three factors: strain-strangled voice quality, glottal fry and monopitch. However, greater separation was obtained between the three groups using the direct method of discriminant analysis which yielded eigenvalues of 45.86 and 19.53 with p values of .002 and .037. This analysis included 16 of the 19 speech attributes and provided 100% separation between the three groups (SDS, parkinsonian, and normal controls).

DISCUSSION

Well over 100 cases with the spectrum of symptoms which Shy and Drager correlated with multiple system pathology have now been described. The symptoms of autonomic failure, pyramidal disease, and cerebellar dysfunction have been associated with pathology of the pigmented nuclei and including the dorsal motor nucleus of the vagus.[8] Two cases requiring tracheostomy have been previously reported.[9,10]

Vocal fold function is affected to varying degrees in many cases of Parkinson disease and at least two cases have been described which progressed to glottic obstruction.[11] This glottic obstruction was described as the result of vocal fold spasm. Vas[11] concluded that the spasm was due to basal ganglion disease. Cisler[12] observed diminished vocal fold mobility in one half of his postencephalitic Parkinson patients. Schilling[13] described vocal fold "rigor" with dominance of the adductors. Parkinson himself referred to a patient who, as described, "fetched his breath rather hard."[14] Although we have observed involuntary glottic closure in postencephalitic Parkinson patients with possible tremor of the laryngeal muscles, patients with idiopathic hypokinetic parkinsonism, in our experience, display no involuntary closure. They often exhibit signs of marked rigidity of cricothyroid function, a high



Mean mode ratings for Shy-Drager patients, Parkinson patients and normal controls on the 12 speech attributes found to differ between Shy-Drager patients and age- and sex-matched normal controls and Parkinson patients.

fundamental frequency and reduced range in fundamental frequency.[15]

Vocal cord spasm was not seen in the SDS patients involved in this study. Rather, the deficiency was a lack of abductor control. Although vocal fold function may be affected by the extrapyramidal and cerebellar disorders associated with SDS, the abductor paresis appears to be particularly characteristic and severe in this syndrome. All our patients had other evidence of vagal nuclei lesions as well.

The apparently high incidence of glottic obstruction seems to have been frequently overlooked in previous reports of SDS. One report described severe respiratory obstruction in two patients thought to be due to disturbance of the pneumotaxic center even though stridor was present.[4] The glottic obstruction may have been overlooked due to weakness of respiratory musculature often seen in advanced cases of SDS.

Patients with poor laryngeal control due to central neurologic disease may be misdiagnosed as exhibiting vocal cord paralysis due to peripheral nerve involvement. Repeated examinations aided by cine or video documentation allows differentiation between abnormalities associated with different foci of neurologic lesions. Patients with upper motor neuron disease involving lesions of the extrapyramidal system and those with involvement of the cerebellar pathways have deficits in voluntary laryngeal control characterized by uncontrolled, slow or inappropriate movement — not by a lack of movement. Only lower neuron lesions result in the complete absence of laryngeal movement.

The motor fibers of the vagus nerve controlling laryngeal abduction arise in the nucleus ambiguus[16] and probably also the retrofacial nuclei of the medulla.[17] Severe degeneration in the pigmented dorsal nucleus, the vagal parasympathetic center, has been described as characteristic in patients SDS[9] but there is little information on the specific pathology of the vagal centers supplying motor control to the laryngeal muscles. Degeneration in these nuclei with impaired extrapyramidal function is most likely responsible for vocal fold paresis and the poor palatal and pharyngeal control that characterize these patients.

The presentation of unilateral abductor paresis in two patients later progressing to bilateral paresis is suggestive of a progressive lower motor lesion in the brainstem. The abductor neurons and adductor neurons may have anatomically separate origins in the motor nucleus of the vagus. Gacek's[18] work in the cat indicates that the number of abductor fibers is approximately one half that of adductor fibers although this may not be the case in man. Thus differential involvement of abductor function could be the result of either a focal lesion of the abductor nuclei or diffuse involvement resulting in a relative sparing of adductor fibers. The characteristic finding of progressive abductor paresis in this syndrome would seem to indicate the latter possibility and is more consistent with the diffuse involvement that has been described pathologically.[8]

The involvement of abductor function with relative sparing of adductor function resulted in certain characteristic impairments in speech production in these patients, when contrasted with patients with hypokinetic Parkinson disease and normal controls. Vocal symptoms included a wet hoarseness and glottal fry or diplophonia. Glottal fry occurs at the low end of normal speakers' fundamental frequency range in association with reduced subglottal pressure. Thus either a loss in vocal cord tension or respiratory impairment could account for increased occurrence of this type of phonation. The respiratory musculature weakness of SDS patients could reduce subglottal pressure although a reduction in vocal cord tension could also account for increased glottal fry in these patients. Although vocal cord tension is primarily controlled by the cricothyroid, stabilization of the arytenoids by both adductor and abductor muscle contractions may also be necessary for tensing the vocal folds. Although Guidi et al[6] reported primary involvement of the posterior cricoarytenoid in all five Shy-Drager cases, they also reported involvement of the only adductor muscle studied in two of their cases. Involvement of either the adductor or abductor muscles or both may contribute to poor vocal cord tension in this syndrome. Hypokinetic parkinsonian patients frequently have breathy voices and poor pitch control but have full adductor and abductor motion[7] and are without wet hoarseness or glottal fry abnormalities.

The other symptoms associated with SDS, not found in Parkinson disease, included a slow speech rate, and an equal stress on all syllables. A more fine-grained analysis of speech-production timing is necessary to determine whether these symptoms are the result of extensive lower motor neuron disease affecting tongue, lip and palatal movement control,[7] or due to vocal fold paresis alone altering speech rate.

The remainder of speech impairments associated with SDS were found to be similarly impaired in Parkinson disease and, therefore, are most likely due to the extrapyramidal involvement in this disorder. These included strained-strangled and breathy voice quality, imprecise consonants, monopitch, monoloudness, reduced stress and reduced intensity. Most of these symptoms imply impaired vocal cord adduction and rigidity of the tensor control musculature.

In conclusion, both extrapyramidal and bulbar involvements were found to affect vocal control, although the symptom complexes were dissimilar. A previous study has reported the multiple dysarthric symptom complexes associated with SDS.[19] However, when this syndrome was compared with other forms of extrapyramidal disease, the additional vocal and speech symptoms due to brainstem pathology became apparent. The diagnosis Shy-Drager syndrome should be considered whenever a patient is referred with symptoms of orthostatic hypotension, laryngeal stridor, restriction in range of vocal cord abduction either unilaterally or bilaterally, vocal hoarseness, intermittent diplophonia and a slow speech rate.

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REFERENCES

1. Shy GM, Drager GA. A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study. Arch Neurol 1960; 2:511-27.

2. Hughes RO, Cartlidge NEF, Millac P. Primary neurogenic orthostatic hypotension. J Neurol Neurosurg Psychiatry 1970; 33:363-71.

3. Williams A, Hanson D, Calne DB. Vocal cord paralysis in the Shy-Drager syndrome. J Neurol Neurosurg Psychiatry 1979; 42:151-3.

4. Bannister R, Oppenheimer DR. Degenerative diseases of the nervous system associated with autonomic failure. Brain 1972; 95:457-74.

5. Spokes EGS, Bannister R, Oppenheimer DR. Multiple system atrophy with autonomic failure. J Neurol Sci 1979; 43: 59-82.

6. Guidi GM, Bannister R, Gibson WPR, Payne JK. Laryngeal electromyography in multiple system atrophy with autonomic failure. J Neurol Neurosurg Psychiatry 1981; 44:49-53.

7. Darley FL, Aronson AE, Brown JR. Motor speech disorders. Philadelphia: WB Saunders, 1975.

8. Vanderhagen JJ, Perier O, Sternon JE. Pathological findings in idiopathic orthostatic hypotension. Its relationship to Parkinson's disease. Arch Neurol 1971; 24:207-14.

9. Roessmann U, Van Den Noorst S, McFarland DE. Idiopathic orthostatic hypotension. Arch Neurol 1977; 24:503-10.

10. Israel RH, Marion JM. Upper airway obstruction in the Shy-Drager syndrome. Ann Neurol 1977; 2:83.

11. Vas CJ, Parsonage M, Lord OC. Parkinsonism associated with laryngeal spasm. J Neurol Neurosurg Psychiatry 1965; 28:401-3.

12. Cisler J. Sur les troubles du language articule et de la phonation au cours de l'encephalite epidermique. Arch Int Laryngol 1927; 33:1054-7.

13. Schilling R. Experimentell-phonetische Untersuchungen bei Erkrankungen des extrapyramidalen Systems. Arch Psychiatr Nervenkr 1925; 75:419-71.

14. Parkinson J. An essay on the shaking palsy. Arch Neurol Psych 1922; 7:681-710.

15. Canter GJ. Speech characteristics of patients with Parkinson's disease. I. Intensity, pitch and duration. J Speech Hear Dis 1963; 28:221-9.

16. Haymaker WE. Localisation of lesions involving cranial nerves IX through XII. In: Bing's local diagnosis in neurological diseases. 15th ed. St. Louis: CV Mosby, 1969:170-85.

17. Gacek RR. Localization of laryngeal motor neurons in the kitten. Laryngoscope 1975: 85:1841-61.

18. Gacek RR. Localization of adductor and abductor motor nerve fibers of the larynx. Ann Otol Rhinol Laryngol 1977; 86: 770-6.

19. Linebaugh C. The dysarthrias of Shy-Drager syndrome. J Speech Hear Dis 1979; 44:55-60.

APPENDIX

DEFINITIONS OF SPEECH RATINGS

Attribute	*Definition*	*Interclass Correlation Coefficient*
Harshness	Voice is harsh, rough and raspy	.95
Inappropriate silences	Inappropriate silent intervals	.99
Variable rate	Rate alternates between slow and fast	.99
Increasing rate	Rate becomes increasingly fast within connected speech	.72
Short rushes	Short rushes of speech separated by pauses	1.00
Nasality	Voice sounds excessively nasal. Excessive amount of air is resonated by nasal cavities	.93
Uncontrolled pitch variation	Pitch of the voice shows sudden and uncontrolled variation (falsetto breaks) or waver and modulation of pitch	.96
Uncontrolled loudness variation	Voice shows sudden, uncontrolled alterations in loudness, sometimes becoming too loud or too weak	.97
Wet hoarseness	Wet, liquid-sounding hoarseness	.96
Glottal fry (diplophonia)	Bubbly, crackling low pitched phonation	.92
Strain strangle	Voice sounds like an effortful squeezing of voice through the glottis	.88
Breathy	Breathy, weak, thin	.96
Imprecise consonants	Consonant sounds are slurred, distorted, lack crispness and run into each other	.96
Monopitch	Voice lacks normal pitch and inflectional changes	.93
Monoloudness	Voice lacks normal variations in loudness	.96
Reduced stress	Speech shows reduction of proper stress on emphasis patterns	.95
Excess stress	Excess stress on usually unstressed parts of speech	.86
Intensity	Intensity is either too low or too high in relation to a constant reference synthesized vowel	.99
Rate	Rate of speech is abnormally slow or too rapid	.97
Pitch level	Pitch of voice sounds consistently too low or too high for individual's age and sex.	.99

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ORGANIC ACIDS AND ANAEROBIC MICROORGANISMS IN THE CONTENTS OF THE CHOLESTEATOMA SAC

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Organic acids in the contents of the cholesteatoma sac from 28 cases were studied by gas chromatographic technique. Five volatile fatty acids (acetate, propionate, isobutyrate, butyrate and isovalerate) and lactate were detected in large amounts, which may lower the pH of the cholesteatoma content. These acids were considered to be derived from products of anaerobic microorganisms. Therefore, the contents from 12 cases were cultured anaerobically in a glove box. Obligate microorganisms were identified in 92% of the cases and *Peptococcus*, *Bacteroides*, and *Clostridium* species were frequently isolated. In vitro, such obligate anaerobes produced various organic acids from the cholesteatoma content. Facultatives such as *Staphylococcus aureus* and *Proteus mirabilis* produced acetate in the content under aerobic and anaerobic conditions, whereas no organic acid was produced by *Pseudomonas aeruginosa*. Organic acids in the cholesteatoma content could be fermentative products made by the microorganisms, anaerobes and facultatives, which use the content as a substrate for acid production.

INTRODUCTION

The mechanism of bone destruction in cholesteatoma otitis has been discussed by many investigators. Sadé et al[1] pointed out that the cellular and keratin debris in cholesteatoma is an ideal culture media for bacteria, and bone resorption associated with cholesteatoma is usually accompanied by bacterial infection. Kaneko et al[2] examined the bone resorption in cholesteatoma histologically, and found that the cholesteatoma content which escaped into the subepithelial layer through the rupture of cholesteatoma epithelium induced characteristic granulation tissue in the subepithelial layer and that bone resorption occurred in the vicinity of the rupture site. Bernstein et al,[3] showed that cholesteatoma tissue produced significant ^{45}Ca release from an embryonic bone during tissue culture, and suggested that a soluble product from a cholesteatoma is capable of calcium resorption of a bone, of osteoclastic activation and of inhibition of bone synthesis.

The contents of the cholesteatoma sac include keratin and lipids, such as cholesterol, phospholipids of epithelial origin and microorganisms. Takayama[4] analyzed the chemical composition of the cholesteatoma content and reported that the content in dry weight was composed of 40.5% protein and 25.8% lipid which included cholesterol, phospholipid, free fatty acid and neutral fat. Recently, Yuasa et al[5] using the microcombination glass pH probe found that the cholesteatoma contents from ten patients showed acidity ranging from pH 4.35 to 6.85. They suspected that the cornified material might play an important role in bone destruction observed in cholesteatoma otitis.

On the other hand, it is well known that acids are essential for demineralization of hard tissue, eg, citric and/or lactic acid in osteoclastic bone resorption,[6,7] or organic acids produced by oral microorganisms in dental caries.[8] The acidity in the cholesteatoma content may also be due to the metabolic end-products of facultative and anaerobic microorganisms. More importantly, it is said that anaerobic microorganisms have the ability to produce various kinds of organic acids.

In this study, the detection of organic acids and the identification of the anaerobic microorganisms in the cholesteatoma content were carried out, and the mechanism of acid production was investigated.

MATERIALS AND METHODS

Chemicals. We utilized the following materials in our study: Trypticase peptone (BBL, Division of Becton, Dickinson & Co), brain heart infusion (BHI), (Difco), sodium acetate, sodium pyruvate, sodium citrate, lithium lactate, isobutyric acid, isovaleric acid, valeric acid, isocapronic acid, capronic acid, succinic acid and malic acid (Wako Pure Chemical Industries, Osaka, Japan), and sodium propionate (Daiichi Pure Chemicals, Tokyo).

Preparation of the Cholesteatoma Content. Cholesteatoma tissue was obtained from 28 patients at the time of surgery. Each content of cholesteatoma was carefully separated from the surrounding tissues, such as epithelia, granulations and bones, and after measuring its wet weight, it was homogenized with distilled water or with 0.9% NaCl solution (the concentration was about 100-200 mg wet weight of the content).

Assay of Organic Acids in the Cholesteatoma Content. Volatile fatty acids (C_2-C_6), acetoin, diacetyl, alcohols (C_2-C_5), lactate, and succinate were assayed by the gas chromatographic procedure on a chromosorb 101 at 200°C with a flame ionization detector and showed a single peak.[9] In our investigation, pyruvate, citrate and malate also gave a single peak using this method. To acidify the homogenized sample, one-ninth volume of 25%

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TABLE 1. VOLATILE FATTY ACIDS IN CHOLESTEATOMA CONTENT (N = 28)

	No. of Cases	Range*	Mean*
Acetate	23	0-138.0	17.5
Propionate	16	0-13.0	2.6
Isobutyrate	9	0-6.3	1.1
Butyrate	15	0-22.0	4.1
Isovalerate	6	0-13.0	0.9

*nmol/mg wet weight of the cholesteatoma content.

(wt/vol) metaphosphoric acid solution was added,[10] and after centrifugation, 5 µl of the supernatant of the sample was injected directly into the column of gas chromatograph. The peaks of the chromatograms can be determined qualitatively and quantitatively in comparison with a known amount of the standard solution.

Identification of Anaerobic Microorganisms in the Cholesteatoma Content. The cholesteatoma contents were obtained from 12 patients at the time of surgery. The content was immediately placed in a screw-capped tube filled with CO_2 and H_2, and the tube was transported into the anaerobic glove box in an atmosphere of 10% CO_2 and 10% H_2 in nitrogen.[11] The following procedures were done in the anaerobic globe box. The content was homogenized with 0.9% NaCl solution, and a serial 10-fold dilution was made from the homogenate. Subsequently, 0.1 ml of each dilution was spread over the duplicated BHI-yeast extract blood agar plate, and cultured at 37°C under anaerobic conditions. The anaerobic microorganisms were isolated and purified, and the obligate anaerobes were identified by the methods of Holdemann and Moore.[12]

Organisms for Incubation with the Cholesteatoma Content. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Proteus mirabilis*, obtained at the central laboratory, Tohoku University Hospital, were isolated from the lesion of cholesteatoma otitis via the external auditory canal, and cultured in peptone yeast glucose (PYG) broth at 37°C under aerobic conditions for about 24 hours. Among the anaerobic bacterias isolated from the cholesteatoma content as previously described, *Bacteroides melaninogenicus* and *Clostridium difficile* were selected for culture in BHI broth at 37°C for 24 to 48 hours under anaerobic conditions.

Assays of Bacterial End-products in Incubation with the Cholesteatoma Content. Microorganisms of each species were washed twice with 0.9% NaCl solution and resuspended with the same solution to give a turbidity of 30 at 660 nm. The contents, homogenized with 0.9% NaCl solution, were frozen and stored at −20°C until the study was performed.

The reaction was started by mixing 150 µl of the bacterial suspension, 250 µl of homogenized content, and 50 µl of 0.1M potassium phosphate buffer solution (pH 7) containing 10 mM $MgCl_2$. For controls, either a bacterial suspension or a homogenized content was replaced by an identical amount of 0.9% NaCl solution. The reaction mixture containing *P aeruginosa*, *S aureus* and *P mirabilis*, was incubated in a 10 ml Erlenmyer flask, shook in the water bath at 37°C under aerobic conditions, and the reaction was stopped at 0, 15, and 30 minutes to add 50 µl of 25% metaphosphoric acid solution to the mixture. The reaction mixture containing *S aureus*, *P mirabilis*, *B melaninogenicus* and *C difficile* was initiated in a 10 ml screw-capped tube placed in the thermostated brock heater of 37°C in the anaerobic glove box. The reaction was stopped at 0, 3, and 6 hours, to add metaphosphoric acid as mentioned above. All of the reaction mixtures were centrifuged and the supernatant fluids were analyzed for detection of organic acids by gas chromatographic procedure as previously described.

TABLE 2. CULTURE RESULTS (N = 12)

	No. of Cases
No growth	0
Facultatives present	11
Anaerobes present	11
Species 1	6
Species 2	3
Species 3	1
Species 4	0
Species 5	1
Both present	10

TABLE 3. ANAEROBIC MICROORGANISMS ISOLATED FROM CHOLESTEATOMA CONTENT

Anaerobes	No. of Cases
Gram-positive cocci	
Pc magnus	2
Pc saccharolyticus	2
Pc morbillorum	1
Pc niger	1
Ps micros	1
Gram-negative cocci	
Veillonella	2
Gram-positive rods	
C difficile	2
C sp*	1
E tortuosum	1
P acnes	1
Gram-negative rods	
B melaninogenicus	3
B coagulans	1
Fusobacterium sp*	1

* Species not identified.

RESULTS

Organic Acids in the Cholesteatoma Content. The composition of the volatile fatty acids in the 28 samples studied are shown in Table 1. Five kinds of volatile fatty acids, acetate (C_2), propionate (C_3), isobutyrate (C_4), butyrate (C_4), and isovalerate (C_5) were identified in these samples. Lactate (nonvolatile fatty acid) was detected in only one sample. Acetate was identified in 23 samples out of 28 and its content tended to be greater than that of the other acids. Propionate and butyrate were detected in more than half of the samples, and isobutyrate and isovalerate existed in some samples. Other volatile fatty acids (valerate, isocapronate and capronate), and nonvolatile fatty acids, (succinate, pyruvate, citrate and malate) were not detected.

Obligate Anaerobes in Cholesteatoma Content. Anaerobic microorganisms were isolated from 11 patients out of 12 (92%), and facultatives were also detected in 11 patients (92%). None of the samples was free from the microorganisms, and in ten patients (83%), both anaerobes and facultatives were present (Table 2). The number of organisms in each sample identified varied between 1-5 species, and in half of the patients, only one species of anaerobes could be identified. Table 3 shows species of the anaerobic microorganisms identified from the 12 patients in this study. *Peptococcus* sp were most frequently isolated followed by *Bacteroides* sp. B melaninogenicus was isolated from three cases.

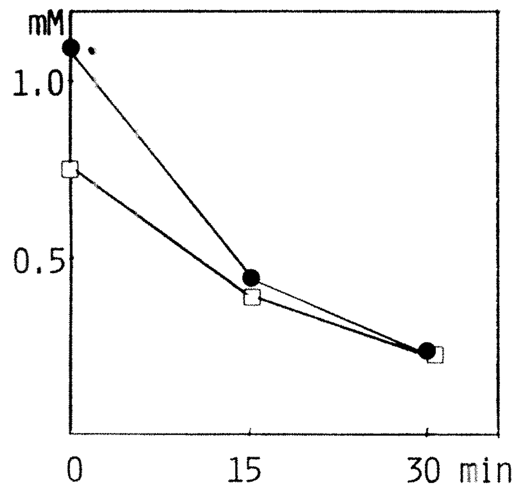

Fig. 1. Concentration of volatile fatty acids in reaction mixture of bacterial suspension and homogenized content plotted against incubation time. *Pseudomonas aeruginosa* (aerobic). ● - Acetate; □ - Butyrate.

Bacterial End-products after Intubation with the Cholesteatoma Content. Figures 1-5 show the time course of volatile fatty acid concentrations in the reaction mixture in which the bacterial suspensions were incubated with the homogenate of the cholesteatoma content under aerobic and/or anaerobic conditions at 37°C. When *P aeruginosa* was incubated with the content, acetate and butyrate which had been present before incubation decreased gradually in quantity (Fig. 1). In the incubation of *S aureus*, acetate was produced under both aerobic and anaerobic conditions, and isovalerate also slightly increased in the reaction mixture (Fig. 2A, B). Acetate was produced by *P mirabilis* in a fairly large amount under both aerobic and anaerobic conditions, while propionate and butyrate were slightly reduced in quantity (Fig. 3A,B).

Figure 4 shows that *B melaninogenicus* produced four kinds of volatile fatty acids, acetate, propionate, isobutyrate, and isovalerate, from the homogenized content under anaerobic conditions, and that the concentration of butyrate which had been present in the content prior to incubation stayed almost the same. The end-products of *C difficile* from the content included a combination of propionate, isobutyrate, butyrate, isovalerate, valerate, isocapronate and a great amount of acetate (Fig. 5).

In the two control studies, ie, when either bacter-

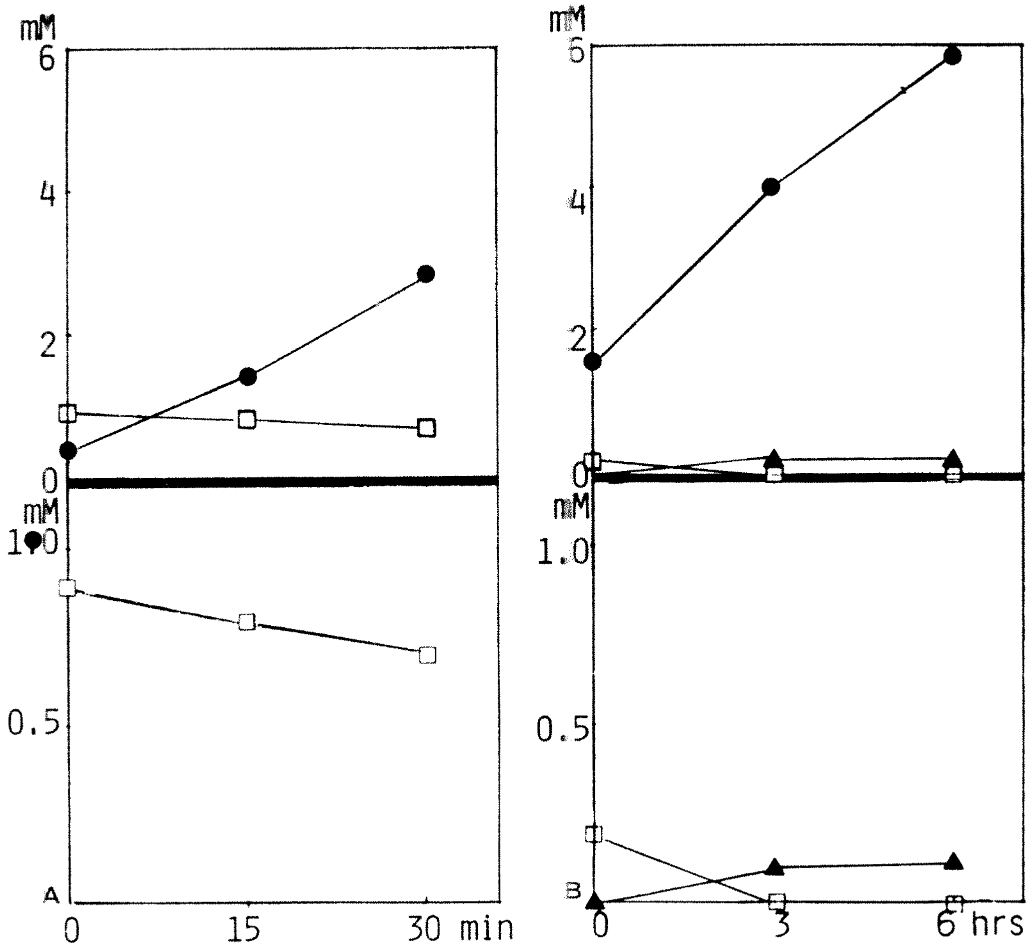

Fig. 2. Time course of concentrations (see Fig. 1 legend). *Staphylococcus aureus.* A) Aerobic; B) Anaerobic. ▲ - Isovalerate.

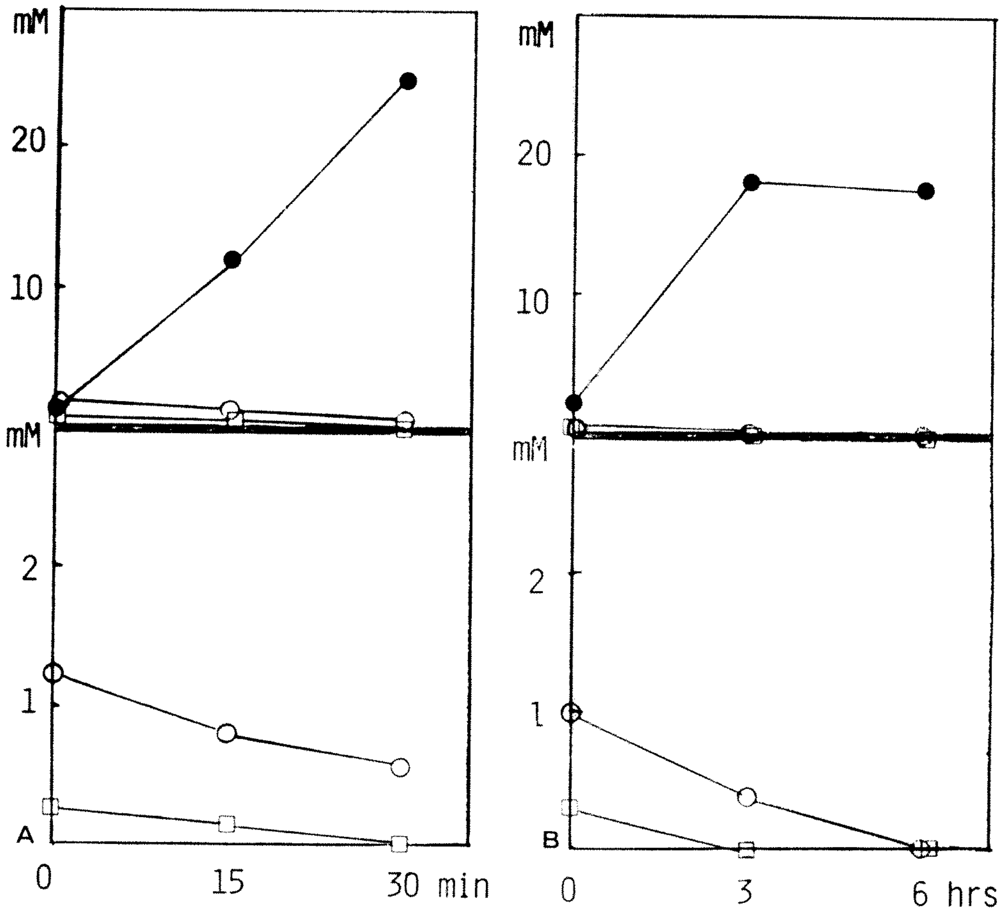

Fig. 3. Time course of concentrations (see Fig. 1 legend). *Proteus mirabilis.* A) Aerobic; B) Anaerobic. ○ - Propionate.

ial suspension or the homogenized content was omitted from the reaction mixture, none of the organic acid was produced within the reaction time. Before the incubation, the reaction mixture contained volatile fatty acids such as acetate and butyrate (as shown in Table 1). To verify that certain particular microorganisms produce the same acids from the contents of different origins, two completely independent incubations were carried out for each of five kinds of bacterial suspensions under both aerobic and anaerobic conditions. The results of these two experiments were in complete agreement with those of our previously mentioned experiments.

DISCUSSION

In the content of the cholesteatoma sac, five kinds of volatile fatty acids (C_2-C_5) and lactate were detected in fairly large amounts, and these acids might be enough to lower the pH of the cholesteatoma content as pointed by Yuasa et al.[5] For example, aqueous solutions of acetic or butyric acid at the concentration of 10 nmol/mg H_2O and 1 nmol/mg H_2O would show about pH 3.4 and 3.9 respectively. In this study, the acids were detected in the cholesteatoma contents in amounts of at least 2 nmol/mg wet weight. Yuasa et al,[6] could not obtain such a low pH in the cholesteatoma content. Hydrogen ion in the content, therefore, would be buffered with other substances such as amino acids present in the content.

These organic acids seem to have two possible origins: one may be the end-products of microorganisms in the cholesteatoma content and the other may originate from the cholesteatoma epithelium. The cholesteatoma content is not composed of living cells but cell debris, which seems to be unable to produce volatile fatty acid, although it is often accompanied with bacterial infection. *Pseudomonas* sp, *Proteus* sp and *S aureus* were frequently isolated via the external auditory canal in the previous study.[13] In the present study, anaerobes and/or facultatives were found in all cases. It is well known that some of the anaerobic bacteria which were detected in the content have the ability to produce various kinds of organic acids from the culture mediums. Therefore, this characteristic is utilized for the identification of anaerobic microorganisms. For example, *C difficile* produces acetate, propionate, butyrate, isobutyrate, valerate, isovalerate, isocapronate, lactate, and formate from the culture medium such as PYG and BHI broth. *Propionibacterium acnes* produces acetate and propionate, and *B melaninogenicus ss asacchalolyticus* produces acetate, butyrate, isobutyrate and isovalerate. *Peptococcus*

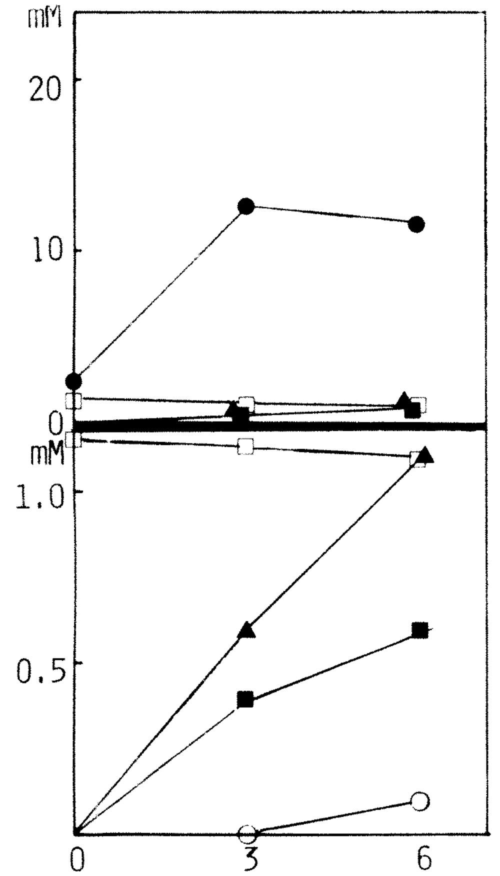

Fig. 4. Time course of concentrations (see Fig. 1 legend). *Bacteroides melaninogenicus* (anaerobic). ■ - Isobutyrate.

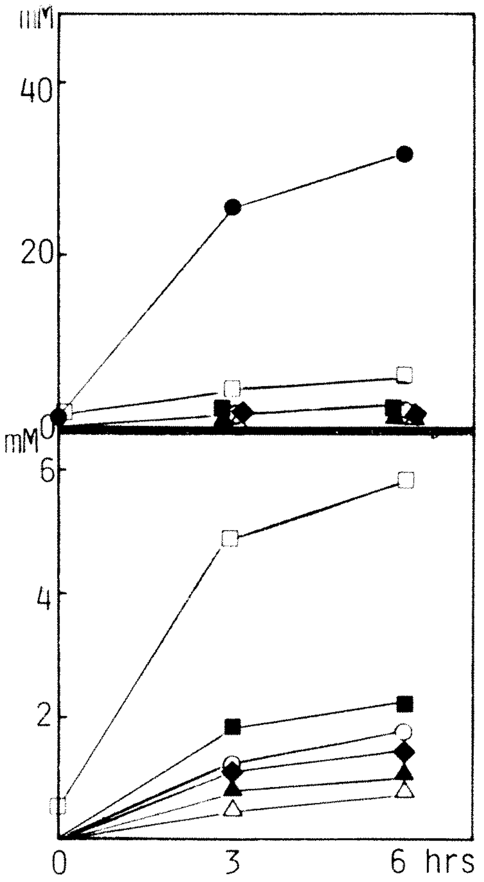

Fig. 5. Time course of concentrations (see Fig. 1 legend). *Clostridium difficile* (anaerobic). △ - Valerate; ◆ Isocapronate.

prevotti produces acetate and butyrate, and furthermore, butyrate is also produced by many anaerobes such as *Fusobacterium* sp and *Eubacterium* sp. Facultative microorganisms, eg, *S aureus* and *P mirabilis* usually produce acids such as acetate and/or lactate from carbohydrates under both aerobic and anaerobic conditions. The incubations in this study showed that the cholesteatoma content could also serve as the substrate for acid-production, at least in vitro, by some of the microorganisms.

Although it is generally accepted that sugars such as glucose can be used as the principal nutrient for almost all microorganisms, the carbohydrates in the cholesteatoma content may not be suitable for the nutrients for the microorganisms, because the carbohydrates in the content may not be in the forms of sugar such as glucose, fructose and maltose, but in those of glycoproteins and glycolipids originated from epithelial membranes. When the concentrations of carbohydrates and proteins in the reaction mixture of *B melaninogenicus* and the cholesteatoma content were assayed before and after the incubations, the concentrations of carbohydrates did not change remarkably, whereas those of proteins gradually decreased in quantity in the reaction mixture (unpublished data). The protein, therefore, might contribute to the source of volatile fatty acids.

Lactate, which plays the most important role in demineralization of dental enamel,[8] was identified in only one sample out of 28 examined. It may be possible that the lactate-consuming microorganisms such as *Veillonella*[14] or *Propionibacterium*,[15] which were actually isolated in our study, used the lactate up, or that the content is not suitable for the production of lactate.

In this study, anaerobic microorganisms were identified in 11 patients out of 12 (92%), and this result showed the fact that anaerobes were found to be considerably more common in cholesteatoma than has been previously reported. Tanahashi et al[16] isolated anaerobes from 3 cases out of 19 of cholesteatoma (17%), and Harker et al[17] found them in the cholesteatoma tissue of two thirds of 30 cases. *Bacteriodes* sp and *Peptococcus* sp were frequently identified and the similar kinds of anaerobes were also isolated as reported by Harker et al. The main reason for the high isolation rate of obligate anaerobes in this study may be due to the use of the anaerobic glove box, and to the improvement of culture methods. It is natural that the anaerobes were frequently found in the cholesteatoma sac because it lacks enough blood supply and air ventilation, however, obligate aerobic bacteria, such as *Pseudomonas* sp required oxygen to resolve the substrate completely to water and carbon dioxide present at the site near the external auditory canal.

The organic acids and anaerobic microorganisms detected in the cholesteatoma content may play an important role in the bone resorption in cholesteatoma otitis when the content flows into the subepithelial layer, through the rupture of the choleateatoma epithelium.[2] Some of the microorganisms in the content were reported to contain the factors causing bone resorptions, ie, endotoxins contained in the cell walls of Gram-negative bacteria such as *Fusobacterium*, *Veillonella* and *Bacteroides*,[18] and lipoteichoic acid which is found in the cell walls of many Gram-positive bacteria.[19] Collagenase and proteolytic enzyme of *Clostridium* sp and *B melaninogenicus*[20] may also contribute to the bone resorption. Osteoclast activating factors through immunological response to some microorganisms are also reported.[21] Organic acids may induce not only the inflammation of the soft tissue, but also the demineralization of the bone, because of their acidity. In this study, we detected the organic acids in the cholesteatoma content and showed that these acids could be the fermentative products of the microorganisms, anaerobes and facultatives, which utilized the components of the contents, perhaps some proteins. However, further investigation is necessary to determine whether or not the cholesteatoma content directly causes bone resorption and what component plays the actual role in bone resorption.

ACKNOWLEDGMENT — We wish to express our thanks to Dr. Tadashi Yamada of the Department of Biochemistry, Tohoku University School of Dentistry and Dr. Kazutomo Kawamoto of the Department of Otolaryngology, Tohoku University, for their constant and valuable advice.

REFERENCES

1. Sadé J, Halevy A. The aetiology of bone destruction in chronic otitis media. J Laryngol Otol 1974; 88:139-43.

2. Kaneko Y, Yuasa R, Ise I, et al. Bone destruction due to the rupture of a cholesteatoma sac. A pathogenesis of bone destruction in aural cholesteatoma. Laryngoscope 1980; 90:1865-971.

3. Bernstein JM, Hausmann E, Wright J. Middle ear disease; release of soluble factor(s) stimulating bone resorption. In: McCabe BF, Sadé J, Abramson M, eds. Cholesteatoma: first international conference. Birmingham: Aesculapius Publishing Company, 1977:152-61.

4. Takayama M. The analysis of cholesterol in cholesteatoma. J Otolaryngol Jpn 1973; 76:636-49.

5. Yuasa R, Kaneko Y, Takasaka T, Iino Y, Tomioka S, Hanajima T. The significance of keratinization in the mechanism of bone destruction in cholesteatoma. In: Sadé J, ed. Cholesteatoma and mastoid surgery. Amsterdam: Kugler Publications; 1982:419-27.

6. Vaes G. On the mechanisms of bone resorption. The action of parathyroid hormone on the excretion and synthesis of lysosomal enzymes and on the extracellular release of acid by bone cells. J Cell Biol 1968; 39:676-97.

7. Borle AB, Nichols N, Nichols G Jr. Metabolic studies of bone *in vitro*. I. Normal bone. J Biol Chem 1960; 235:1206-10.

8. Moore BW, Carter WMJ, Dunn JK, Fosdick LS. The formation of lactic acid in dental plaques. J Dent Res 1956; 35:778-85.

9. Carlsson J. Simplified gas chromatographic procedure for identification of bacterial metabolic products. Appl Microbiol 1973; 75:287-9.

10. Yamada T, Carlsson J. Regulation of lactate dehydrogenase and change of fermentation products in streptococci. J Bacteriol 1975; 124:55-61.

11. Hoshino E, Yamada T, Karino H. Metabolisms of lactate by human dental plaque and Veillonella. Under aerobic and anaerobic conditions. Arch Oral Biol 1982; 26:17-22.

12. Holdemann LV, Moore WEB. Anaerobe laboratory manual. 3rd ed. Blacksburg, Virginia: Virginia Polytechnic Institute and State University, 1975.

13. Karma P, Palva M, Kärjä J. An analysis of mastoid cholesteatomas. Laryngoscope 1977; 87:1559-71.

14. Foubert EL, Douglas HC. Studies on the anaerobic micrococci: the fermentation of lactate by Micrococcus lactilyticus. J Bacteriol 1948; 56:35-6.

15. Van Gent-Ruijters MLW, De Meijere FA, De Vries W, Stouthamer AH. Lactate metabolism in Propionibacterium pentosaceum growing with nitrate of oxygen as hydrogen acceptor. J Microbiol Serol 1976; 42:217-28.

16. Tanahashi S, Suzuki T, Ito H, et al. Anaerobic microorganisms in the ear diseases. Clin Otol Jap 1980; 7:232-3.

17. Harker LA, Franklin PK. The bacteriology of cholesteatoma. In: McCabe BF, Sadé J, Abramson M, eds. Cholesteatoma: first international conference. Birmingham: Aesculapius Publishing Company, 1977:264-7.

18. Hausmann E, Luderitz O, Knox K, Weinfeld N. Stimulation of bone resorption by endotoxin and lipoteichoic acid. J Dent Res 1975; 54:B:B94-9.

19. Hausmann E, Raisz LG, Miller WA. Endotoxin: stimulation of bone resorption in tissue culture. Science 1970; 168:862-4.

20. Seiter S. Proteolytic enzymes. In: Perlmann GE, Rorand L, eds. Methods in enzymology. Vol. 19. New York: Academic Press: 1970:613-35.

21. Takazoe I. Aetiology of the peridontal disease. J Jap Assoc Dent Sci 1979; 5:3-8.

PATHOLOGY CONSULTATION

PRIMARY SQUAMOUS CELL CARCINOMAS OF MAJOR SALIVARY GLANDS

JOHN G. BATSAKIS, MD
HOUSTON, TEXAS

Primary squamous cell carcinomas of the major (parotid and submandibular) salivary glands are uncommon neoplasms. Statistics contrary to that statement are tainted by the inclusion of mucoepidermoid carcinomas and, in the instance of the parotid gland, by metastatic carcinomas. The true frequency is less than 1% of all tumors in the parotid gland and approximately 4% for the submandibular gland.

The misconception that *primary* squamous cell carcinomas of the major salivary glands are relatively common neoplasms is taking time to correct.[1] In any event, it is now quite clear that the carcinoma is unusual, especially in the parotid gland.[2-4] Table 1 presents a more accurate representation of the incidence of primary squamous cell carcinoma in the parotid gland. It should be further appreciated that the collective incidence is much lower than the estimated 1.5% given for metastases to the parotid gland from squamous cell skin cancer of the head and neck.[5]

Reasons for the falsely raised incidence relate exclusively to misclassification and misdiagnosis. For the former, inclusion of mucoepidermoid carcinomas (especially high-grade mucoepidermoid carcinomas) is responsible. Misdiagnoses include mucoepidermoid carcinoma, foci of squamous metaplasia, and metastases.

All, or nearly all, of the acceptable primary squamous cell carcinomas of the parotid gland have been well or moderately well-differentiated neoplasms.[1] This histologic feature should serve to assist in distinguishing them from high-grade mucoepidermoid and metastatic carcinomas.

Local recurrence and regional lymph node metastases are the usual outcome for patients with primary squamous cell carcinoma of the parotid gland.[4] Distant metastases are not common.

Primary squamous cell carcinomas of the submandibular gland, although more numerous, are also not common when compared to other primary salivary gland neoplasms of that gland.[6] Table 2 presents the incidence of primary squamous cell carcinomas in the submandibular gland as reported in several series.[7-12]

In contrast to the parotid gland, intraglandular metastases to the submandibular gland should not be a source of serious differential diagnostic difficulties since such a spread is unusual. Metastases to the regional lymph nodes from the primary squamous cell carcinoma are manifested in over two thirds of the cases.

Mention has been made above concerning the rarity of intraglandular metastases to the submandibular gland. Dockerty and Mayo[13] found that in 500 cases of so-called submandibular malignancy 80% were metastatic lesions, usually squamous cell carcinomas drained by submandibular lymph nodes. The metastases were not to the submandibular gland proper but rather to the several groups of submandibular nodes. All of the nodes lie external to the submandibular gland itself. Even the disputed intracapsular group of nodes very likely should be included with the retroglandular group.

Existence of normal lymphoid tissue and *intraglandular* lymph nodes is denied by most authorities and it is the absence of such tissue that is responsible for the paucity of lymphatic metastases to the submandibular gland.[14] The immunity to metastases extends also to hematogenous involvement. Abramson[15] could find only two such cases in a literature review that extended from 1857 to 1969.

Extension of neoplastic disease from contiguous primary neoplasms or lymph nodes with metastases

TABLE 1. INCIDENCE OF PRIMARY SQUAMOUS CELL CARCINOMA OF THE PAROTID GLAND

Investigators	*Parotid Tumors Reported*	*Primary Squamous Cell Carcinomas Reported*
Batsakis et al[1]	580	2 (0.3%)
Eneroth[2]	2,158	7 (0.3%)
Woods et al[3]	1,360	– (1.5%)
Spiro et al[4]	1,875	10 (0.5%)

From the Department of Pathology and Laboratory Medicine, Maine Medical Center, Portland.

REPRINTS — John G. Batsakis, MD, Chairman, Department of Pathology, M. D. Anderson Hospital, Texas Medical Center, Houston, TX 77030.

TABLE 2. INCIDENCE OF PRIMARY SQUAMOUS CELL CARCINOMA OF THE SUBMANDIBULAR GLAND

Investigators	*Submandibular Gland Tumors Reported*	*Primary Squamous Cell Carcinomas Reported*
Spiro et al[7]	217	15 (7.0%)
Eneroth et al[8]	187	11 (6.0%)
Simons et al[9]	128	3 (2.4%)
Conley et al[10]	115	4 (3.5%)
Trail and Lubritz[11]	58	2 (3.5%)
Rafla[12]	35	1 (3.0%)

are the most likely reasons for the finding of malignancy within the parenchyma of the submandibular gland. Even these events are unusual.

SUMMARY

Primary squamous cell carcinomas of the parotid gland and submandibular gland, if properly distinguished from mucoepidermoid and metastatic carcinomas, are among the most uncommon of primary carcinomas of the major salivary glands. In the instance of the parotid gland, the frequency of metastatic squamous cell carcinoma exceeds the incidence of primary squamous cell carcinoma. In the submandibular gland, because of the paucity of intraglandular lymph nodes, metastases to the gland are rare.

REFERENCES

1. Batsakis JG, McClathey KD, Johns ME, Regezi JA. Primary squamous cell carcinoma of the parotid gland. Arch Otolaryngol 1976; 102:355-7.

2. Eneroth C-M. Salivary gland tumors in the parotid gland, submandibular gland, and the palate region. Cancer 1971; 27: 1415-8.

3. Woods JE, Chong GC, Beahrs OH. Experience with 1,360 primary parotid tumors. Am J Surg 1975; 130:460-2.

4. Spiro RH, Huvos AG, Strong EW. Cancer of the parotid gland: a clinicopathologic study of 288 primary cases. Am J Surg 1975; 130:452-9.

5. Ridenhour CE, Spratt JS Jr. Epidermoid carcinomas of the skin involving the parotid gland. Am J Surg 1966; 112:504-7.

6. Marciani RD, Trodahl JN, Dauchess VG, Canlas MS. Squamous cell carcioma of the submandibular gland. J Oral Surg 1976; 34:646-50.

7. Spiro RH, Hajdu SI, Strong EW. Tumors of the submaxillary gland. Am J Surg 1976; 132:463-8.

8. Eneroth C-M, Hjertman L, Moberger G. Malignant tumors of the submandibular gland. Acta Otolaryngol (Stockh) 1967; 64:514-36.

9. Simons JN, Beahrs OH, Woolner LB. Tumors of the submaxillary gland. Am J Surg 1964; 108:485-94.

10. Conley J, Meyers E, Cole R. Analysis of 115 patients with tumors of the submandibular gland. Ann Otol Rhinol Laryngol 1972; 81:323-30.

11. Trail ML, Lubritz J. Tumors of the submandibular gland. Laryngoscope 1974; 84:1225-32.

12. Rafla S. Submaxillary gland tumors. Cancer 1970; 26: 821-6.

13. Dockerty MB, Mayo CW. Primary tumors of the submaxillary gland with special reference to mixed tumors. Surg Gynecol Obstet 1942; 74:1033-45.

14. Staley CJ, Kaupp NA Jr, Fisher E. The submandibular salivary gland in radical neck dissection specimens. Am J Surg 1963; 106:831-4.

15. Abramson AL. The submaxillary gland as a site of distant metastasis. Laryngoscope 1971; 81:793-5.

COMBINED OTOLARYNGOLOGICAL SPRING MEETINGS

The Fairmont Hotel, New Orleans, Louisiana

1983 Preliminary Programs
(Subject to change and Council approval)

AMERICAN NEUROTOLOGY SOCIETY

April 8-9, 1983

Endolymphatic Subarachnoid Shunt. D. E. Brachmann, MD.

Labyrinthine Cryosurgery. R. J. Wolfson, MD.

Cochleostomy. H. F. Schuknecht, MD.

Ultrasonic Irradiation of the Labyrinth. C. L. Pennington, MD.

Surgical Concept in the Pathogenesis of Menière's Disease. M. M. Paparella, MD.

Residency and Fellowship Training in Otology, Neurotology, and Skull Base Surgery. M. D. Graham, MD.

Remarks by the Guest of Honor: Surgical Neurotology. W. F. House, MD.

Acoustic Neuroma Surgery. C. M. Luetje, MD.

Role of the Neurosurgeon in Acoustic Neuroma Surgery. M. B. Camins, MD.

Retrolabyrinthine Eighth Nerve Section. H. Silverstein, MD.

Middle Fossa Surgery. R. T. Miyamoto, MD; S. R. Althaus, MD; D. F. Wilson, MD; K. H. Brookler, MD.

Singular Neurectomy. R. R. Gacek, MD.

Current Concepts in Intratemporal Facial Nerve Surgery. M. D. Graham, MD.

Facial Nerve Neuroma. J. L. Pulec, MD.

Facial Nerve Palsy Recovery Questionnaire. D. E. Brackmann, MD.

Remarks by Guest of Honor: A Generation of Neurotology — Where Do We Fit? W. Rubin, MD.

Vestibular Compensation. J. T. Benitez, MD; K. R. Bouchard, PhD; D. Lane-Szopo.

Remote Monitoring of Evoked Responses. R. J. Keim, MD.

The Dynamic Illegible 'E' Test. N. S. Longridge, MB.

Sensorineural Hearing Loss in Chronic Otitis Media. J. L. Sheehy, MD.

Revision Surgery in Sensorineural Hearing Losses. W. H. Lippy, MD.

Cochlear Implant. W. F. House, MD.

AMERICAN OTOLOGICAL SOCIETY, INC.

April 9-10, 1983

Arachnoid Cyst in the Internal Auditory Canal. H. F. Schuknecht, MD.

Vascular Loop as a Cause of Episodic Vertigo. B. F. McCabe, MD; L. Harker, MD.

Modification in the Management of Petrous Apicitis. R. Chole, MD, PhD; L. Bernstein, MD.

Hearing Loss in Infants — The Cytomegalovirus. D. G. Pappas, MD.

Fractures of the Temporal Bone and Cholesteatoma. J. Freeman, MD.

Juvenile Otosclerosis. M. Robinson, MD.

Minipanel: Stapedectomy — What To Do and What Not to Do. R. J. Bellucci, MD, Moderator; W. H. Lippy, MD; T. Manford McGee, MD.

Care of the Ear Canal and Mastoid Bowl. R. L. Ruggles, MD.

Incus Inter-Position: A Fifteen-Year Report. C. L. Pennington, MD.

The Sleeve Autograft in Congenital Cholesteatoma. R. Wehrs, MD.

Tympanomastoidectomy — A Twenty-Five Year Report. J. M. Cole, MD.

Prolonged Middle Ear Ventilation — Right Tube in Right Place. B. W. Armstrong, MD.

Experiences With the Cochlear Implant in Preschool Children. W. House, MD.

The Deaf Child — Habilitation With and Without the Cochlear Implant. D. Ling, PhD.

Histologic Evaluation of Temporal Bones Following Cochlear Implantation. F. H. Linthicum, Jr, MD.

Electrical Stimulation of the Ear — Experimental Studies. J-M. Aran, PhD; Y. Cazals; R. Charlet de Suvage; M. Portmann, MD.

Cochlear Implant in Nonhuman Primates. J. M. Miller, PhD.

Continuous Noise — Otologist Responsibility. J. Sataloff, MD.

Panel: Management of Sensorineural Hearing Loss. J. L. Sheehy, MD, Moderator; H. A. Ted Bailey, Jr, MD; E. W. Johnson, PhD; T. Manford McGee, MD; J. A. Vernon, PhD.

The Human Round Window — Ultrastructure — Clinical Implications. M. Paparella, MD; P. Schachern, PhD; Y. B. Choo, MD.

Tympanosclerosis — Implications of the Theory of Pathogenesis. M. Schiff, MD.

The Petromastoid Canal. B. Proctor, MD.

Improved BSER in Patients With Cerebellopontine Angle Lesions. M. Møller, MD, PhD; A. Møller, PhD.

The Evaluation of the Auditory System — Where Are We in 1983? D. E. Brackmann, MD.

AMERICAN LARYNGOLOGICAL ASSOCIATION

April 10-11, 1983

Objective Measurement of Voice Pathology. D. G. Hanson, MD; B. R. Gerratt, PhD; P. H. Ward, MD.

Objective and Quantitative Screening of Vocal Cord Function. E. Rontal, MD; M. Rontal, MD; H. J. Jacob, MD; M. Rolnick, PhD.

Videolaryngoscopy — A Comparison of Fiberscopic and Telescopic Documentation. E. Yanagisawa, MD.

Muscle Tension Laryngopathy. M. D. Morrison, MD.

Three-Dimensional Computer Reconstruction of the Neuromuscular Junctions of the Thyroarytenoid Muscle. M. Rosen, MD; L. T. Malmgren, PhD; R. R. Gacek, MD.

Voice Change in the Pediatric Patient: A Differential Diagnosis. S. R. Cohen, MD.

Baker Lecture — Orientation in Flight. R. Malcolm, PhD.

Objective Measurement of Endotracheal Tube Pressures Exerted on Laryngeal Structures. E. A. Weymuller, Jr, MD; M. J. Bishop, MD; A. Hibbard, MD.

Lack of Efficacy of Systemic Antibiotics and Steroids for Acquired Subglottic Stenosis in a Canine Animal Model. J. S. Supance, MD; W. J. Doyle, PhD; J. S. Reilly, MD; C. D. Bluestone, MD; J. Hubbard, MD.

Congenital Laryngeal Hemangiomata. B. Benjamin, OBE, FRACS, DLO; P. Carter, MD.

Further Observations on Interferon (IFN) Treatment of Recurrent Respiratory Papillomatosis (RRP): A Comparison of Finnish Blood Bank and New York Blood Bank Products. R. B. Sessions, MD; H. Goepfert, MD; J. U. Gutterman, MD.

Teflon Injection of the Vocal Cord: Complications, Error and Precaution. R. B. Lewy, MD.

Vocal Ligament Tightening — Early Experiences. F. E. LeJeune, Jr, MD.

Hosmer A. Johnson — A Life to Remember. S. A. Friedberg, MD.

Research Speaker: Can Functional Dysphonia be Investigated? W. H. Perkins, PhD.

Training Singing Children During Prepubertal, Pubertal and Adolescent Phases of Voice Mutation: An Applied Physiologic Seven-Year Study Including 175 Children. I. M. Blatt, MD; C. Astraquillo, Mus D.

Laryngeal Nerve Crush for Spastic Dysphonia. H. F. Biller, MD; M. L. Som, MD.

Effects of Stomach Acid on the Larynx. N. R. Olson, MD.

Muscular Transposition as a Method of Laryngeal Rehabilitation. G. D. Neal, MD; M. Stearns, FRCS; R. Trachy, BS; C. W. Cummings, MD.

Panel on Organic Voice Disorders. H. H. Dedo, MD, Moderator; G. A. Gates, MD; W. Perkins, PhD; H. von Leden, MD; C. W. Vaughan, MD.

Intralaryngeal Release for Tracheal Anastomosis. M. E. Sachs, MD; J. Conley, MD; D. Rabuzzi, MD.

The Radiated Larynx — A Surgeon's Dilemma. J. S. Lewis, MD; T. Kusonruksa, MD.

Preoperative Irradiation and Surgery for Carcinoma of the Base of the Tongue. S. E. Thawley, MD; J. R. Simpson, MD; J. E. Marks, MD; C. A. Perez, MD.

Adenoid Cystic Carcinoma of the Subglottic Region. D. T. Donovan, MD; J. J. Conley, MD.

AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

April 11-13, 1983

Chevalier Jackson Lecture: Congenital Laryngeal Webs. B. Benjamin, FRACS.

Vocal Cord Paralysis Following Intubation. N. L. Cohen, MD; J. Cohen, MD.

Laryngeal Trauma from Short-Term Intubation. J. H. Dickens, MD; S. B. Peppard, MD.

A Comparison of Tracheal Damage from Laser-Ignited Endotracheal Tube Fires. R. H. Ossoff, DMD, MD; J. A. Duncavage, MD; T. S. Eisenman, MD; M. S. Karlan, MD.

Insufflation Anesthesia for Laser Laryngoscopy. T. J. Reichert, MD; T. Johans, MD.

Case Study: Laryngeal Amyloidosis and Laryngocele. J. A. Schild, MD; M. F. Mafee, MD; V. T. Grybauskas, MD.

Sudden Suffocation due to Large Pedunculated Laryngeal Polyp. E. Yanagisawa, MD; J. Hausfeld, MD.

Giant Intraluminal Polyps of the Esophagus. D. P. Vrabec, MD; T. Colley, MD.

Management of Benign Zenker's Diverticulotracheal Fistulae. C. W. Senders, MD; R. W. Babin, MD.

Pneumatic Dilatation as the Primary Treatment for Achalasia. J. B. Jacobs, MD; N. L. Cohen, MD; S. Mattel, MD.

Rehabilitation of Deglutition After Stroke. H. J. Heimlich, MD.

New Instruments:

New Dilatation Tracheoscope. E. T. Edens, MD.

Bidirectional Flow Valve to Reduce Mechanical Dead Space and Adapted to Monitor Gas Pressures in Bronchoscopy of Premature Infants and Neonates. L. Barcliff; J. P. Dudley, MD.

A New Posterior Commissure Laryngoscope for CO_2 Laser Surgery. R. H. Ossoff, DMD, MD; M. S. Karlan, MD; G. A. Sisson, MD.

Research Speaker: The Utility of Bronchoalveolar Lavage in the Diagnosis of Interstitial Lung Disease. W. J. Martin, MD.

The Value of Flexible Fiberoptic Bronchoscopy Without Fluoroscopy in the Diagnosis of Lung Cancer. F. Nagasaki, MD; N. Martini, MD.

Transbronchial Needle Biopsy for Diagnosis and Staging of Bronchogenic Carcinoma. K-P Wang, MD.

The Salivary Scan and Postoperative Fistulization. Lt Col R. K. Newman, USAF, MC, MD; Lt Col F. L. Weiland, USAF, MC, MD; Col P. R. Rosen, USAF, MC, MD; J. T. Johnson, MD; L. W. Gumerman, MD.

Panel, State of the Art — Bronchoscopic Therapy. L. P. Faber, MD, Chairman; D. Cortese, MD; N. Martini, MD; J. H. Harrell, MD; S. Strong, MD.

Laryngeal Spaces. L. W. Welsh, MD.

Tracheostomy in the Morbidly Obese Patient: Problems, Pitfalls and a New Tube Design. C. P. Kimmelman, MD; M. C. Vidas, MD.

The Role of Esophagoscopy in the Evaluation of Patients with Head and Neck Cancer. J. A. Duncavage, MD; T. W. Grossman, MD; R. H. Lehman, MD; T. C. Malin, MA; R. J. Toohill, MD.

Bronchoscopy as an Effective Tool in the Evaluation of Head and Neck Carcinoma. B. Leipzig, MD.

Aortic Wheeze: A Unique Aortic Arch Anomaly Causing Intermittent Tracheal Compression. J. Buckwalter, MD; C. Sasaki, MD; G. Kopf, MD; W. Hellenbrand, MD; C. Kleinman, MD.

Tracheobronchial Compression in Acyanotic Congenital Heart Disease. N. T. Berlinger, MD, PhD; C. Long, MD; J. Foker, MD; R. V. Lucas, Jr, MD.

Congenital Laryngeal Atresia: Histopathologic Study of Two Cases. C. S. Karmody, MD; P. Woo, MD.

Traumatic Hypopharyngeal Pseudodiverticulum in Neonates. J. S. Supance, MD; S. E. Stool, MD.

Unusual Presentations of Penetrating Foreign Bodies of the Aerodigestive Tract. K. Remsen, MD; W. Lawson, MD, DDS; H. F. Biller, MD; M. L. Som, MD.

Bilateral Pneumothorax as the Outcome of the Bronchoscopic Removal of the Fruit of a Puncture Vine. J. P. Dudley, MD.

Ten-Year Review of Tracheotomy. P. Carter; B. Benjamin.

Difficult Laryngoscopy/Intubation: The Child with Mandibular Hyperplasia. S. D. Handler, MD.

Pediatric Endoscopy — Ask the Expert Panel. G. Healy, MD, Chairman.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

April 12-14, 1983

Radiographic Diagnosis of Acoustic Neurinoma. S. G. Harner, MD; D. F. Reese, MD.

New Studies in the Central Auditory Nervous System Indicate How it is Altered After Central or Peripheral Damage and by Experience. M. M. Merzenich, PhD.

Preoperative CT Scan Evaluation for Laryngeal Carcinoma: Correlation with Pathological Findings. L. A. Hoover, MD; T. C. Calcaterra, MD; G. A. Walter, MD; S. G. Larrson, MD.

Ear Disease Among Navajo— A Mass Survey. S. M. Nelson, MD.

Capsular Significance in Parotid Tumor Surgery. D. T. Donovan, MD; J. J. Conley, MD.

Infectious Disease of the Sphenoid Sinus. J. Standefer, MD; G. R. Holt, MD; G. A. Gates, MD.

Panel: Acoustic Neurinoma Diagnosis and Management. W. F. House, MD; R. A. Schindler, MD; M. E. Glasscock, MD.

Mondini's Dysplasia: A Report of Fifteen Cases. D. W. Goin, MD; M. Weaver, MD; R. E. Mischke, MD.

Cinegraphic Observations of Vocal Dysfunction in Parkinson's Disease. D. G. Hanson, MD; B. R. Gerratt, PhD; F. H. Ward, MD.

Explosive Life-Threatening Infections of the Neck. H. J. Beck, MD; J. R. Salassa, MD; T. V. McCaffrey, MD.

Radiographic Findings in Progressive Necrotizing (Malignant) External Otitis. S. D. Gold, MD; P. M. Som, MD; F. E. Lucente, MD; W. Lawson, MD, DDS; S. C. Parisier, MD.

Laser Submucosal Resection of Subglottic or Tracheal Scar with Micro-Trapdoor Flap. H. H. Dedo, MD; C. D. Sooy, MD.

Incidence of Hypothyroidism Following Multimodality Treatment for Advanced Squamous Cell Carcinoma of the Head and Neck. M. R. Posner, MD; T. J. Ervin, MD; D. Miller, MD; R. L. Fabian, MD; C. R. Norris, Jr, MD; R. R. Weichselbaum, MD; C. Rose, MD.

Retropharyngeal Abscess — A Ten Year Experience. C. F. Koopmann, Jr, MD; G. A. Barratt, MD; S. W. Coulthard, MD.

Anatomical-Physiological Correlations in the Vestibular Nerve of the Bullfrog. V. Honrubia, MD; S. T. Sitko; R. Lee; I. R. Schwartz, PhD.

Panel: Chemotherapy in Head and Neck Malignancy. D. Miller, MD.

Otolaryngological Brain Abscess Therapy — Past and Present. B. Brand, MD; R. J. Caparosa, MD; L. G. Lubic, MD.

Selective Management — T_1 Cancer of the Glottis. D. Blakeslee, MD; S. M. Shapshay, MD; G. T. Simpson, MD; C. W. Vaughan, MD; M. S. Strong, MD.

The Role of the Mastoid in Tympanic Membrane Reconstruction. R. K. Jackler, MD; R. A. Schindler, MD.

Auto-Immunity and Inner Ear Disorders. J. E. Veldman, MD, PhD; J. J. Roord, MD; A. F. O'Connor, FRCS; J. J. Shea, MD.

Otosclerosis Versus Otospongiosis: Sequence of. C. Parahy, MD; F. H. Linthicum, Jr, MD.

Injectable Collagen in Laryngeal Rehabilitation. C. N. Ford, MD; D. W. Martin, MD.

The Reliability of Frozen Section Diagnosis of Head and Neck Neoplasms. K. A. Remsen, MD; F. E. Lucente, MD; H. F. Biller, MD.

Panel — Thyroid Disease. Jerome Goldstein, MD.

INSTRUCTIONS TO AUTHORS

Send manuscripts by first class mail to Editor Brian F. McCabe, MD, Department of Otolaryngology-Head and Neck Surgery, University of Iowa Hospitals, Iowa City, IA 52242. Original manuscripts which deal with clinical and scientific aspects of otolaryngology, bronchoesophagology, head and neck, maxillofacial and plastic surgery, audiology, speech pathology and related specialties will be considered for publication. It is understood that manuscripts submitted for review have not been published.

Papers are scheduled for publication in the order of acceptance; however, manuscripts received in improper form require longer production time which may delay publication.

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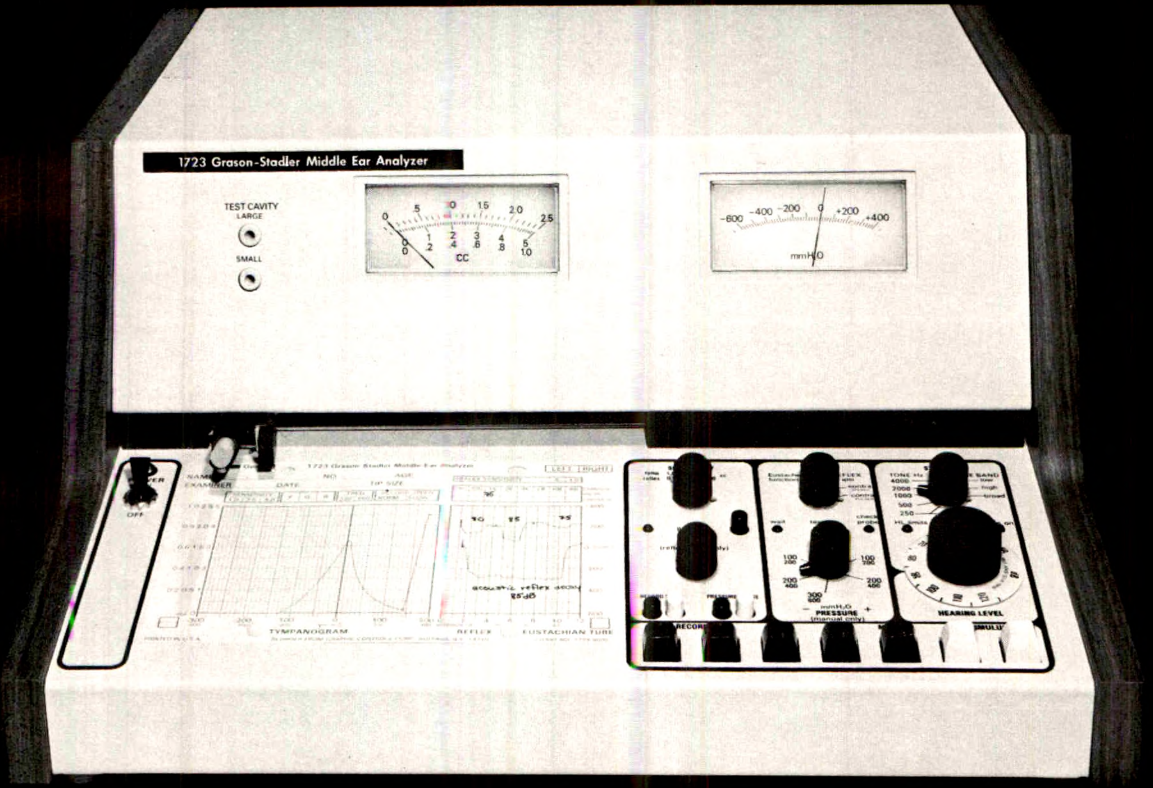

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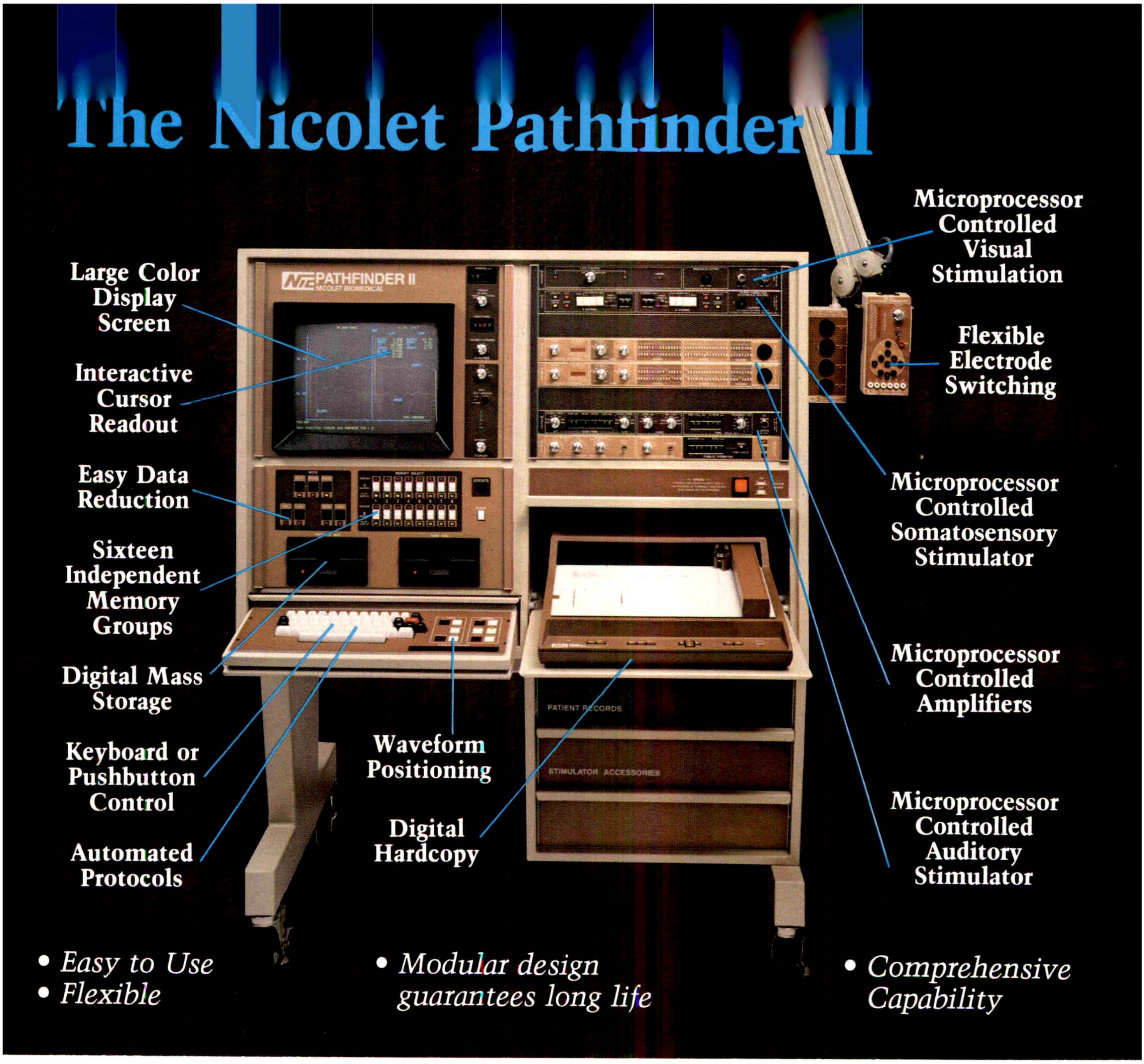
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A160

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For further information contact: Malcolm D. Graham, MD, Dept. of Otorhinolaryngology, University of Michigan Medical Center, Ann Arbor, MI 48109, (313) 764-4131 or (313) 764-8110.

A45

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Ralph A. Nelson, M.D.

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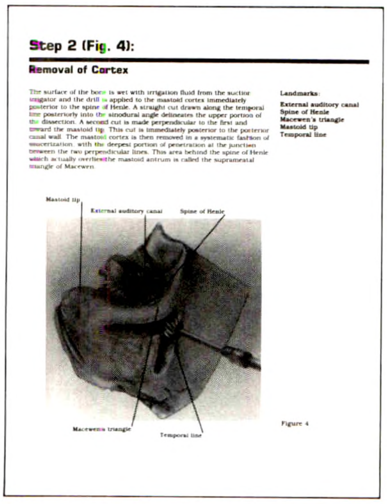

Step 2 (Fig. 4):

Removal of Cortex

The surface of the bone is wet with irrigation fluid from the suction irrigator and the drill is applied to the mastoid cortex immediately posterior to the spine of Henle. A straight cut drawn along the temporal line posteriorly into the sinodural angle delineates the upper portion of the dissection. A second cut is made perpendicular to the first and toward the mastoid tip. This cut is immediately posterior to the posterior canal wall. The mastoid cortex is then removed in a systematic fashion of saucerization, with the deepest portion of penetration at the junction between the two perpendicular lines. This area behind the spine of Henle which actually overlies the mastoid antrum is called the suprameatal triangle of Macewen.

Landmarks:
External auditory canal
Spine of Henle
Macewen's triangle
Mastoid tip
Temporal line

Figure 4

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Fee: US $300

For further information contact: Professor U. Fisch, ENT Department, University Hospital, 8091 Zurich, Switzerland.

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Fee includes lunch each day, dinner Sunday evening and another social evening.

For further information contact: Fred D. Owens, MD, The Dallas Foundation of Otology, 3600 Gaston, Suite 1105, Dallas, TX 75246.

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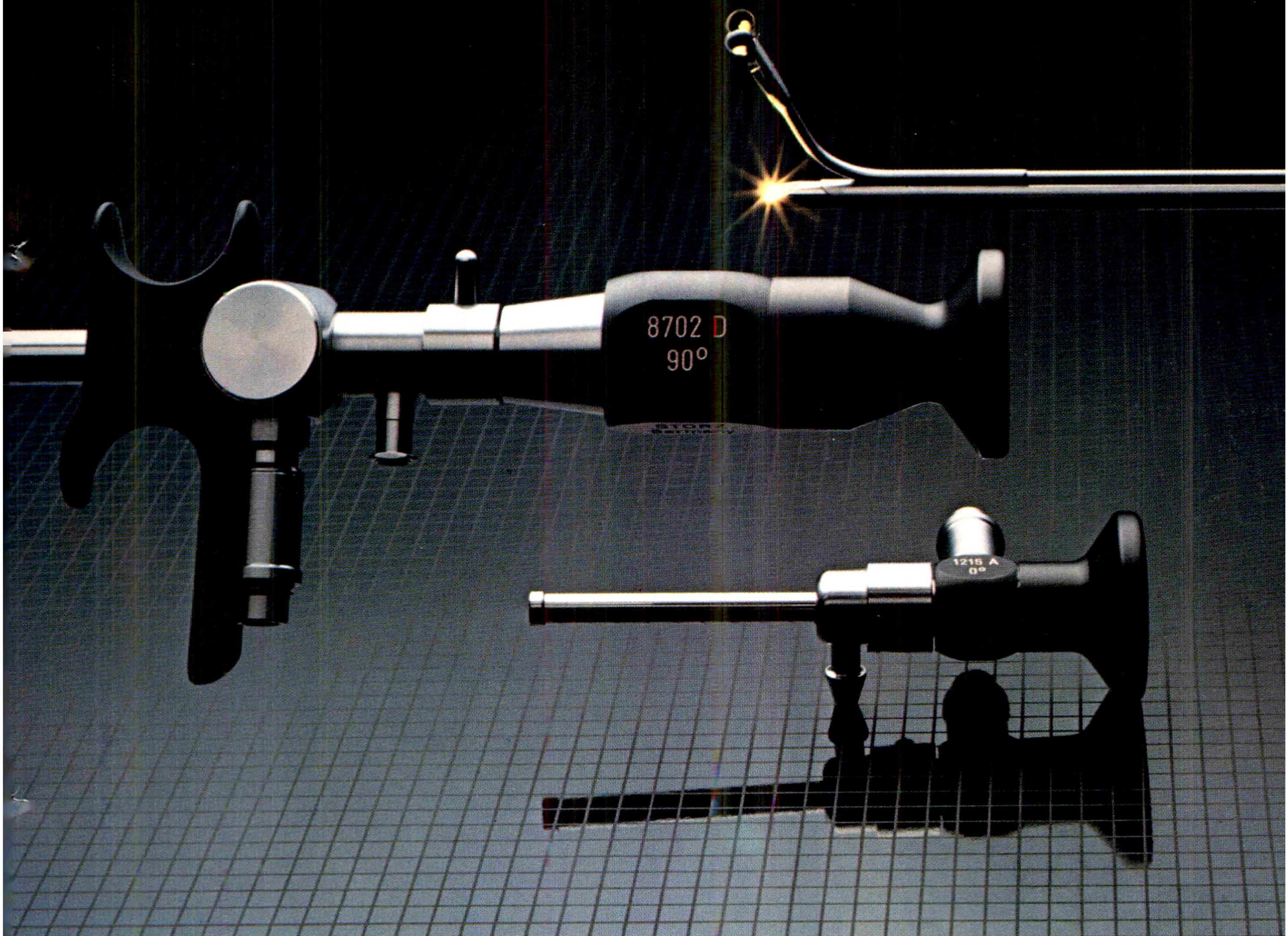

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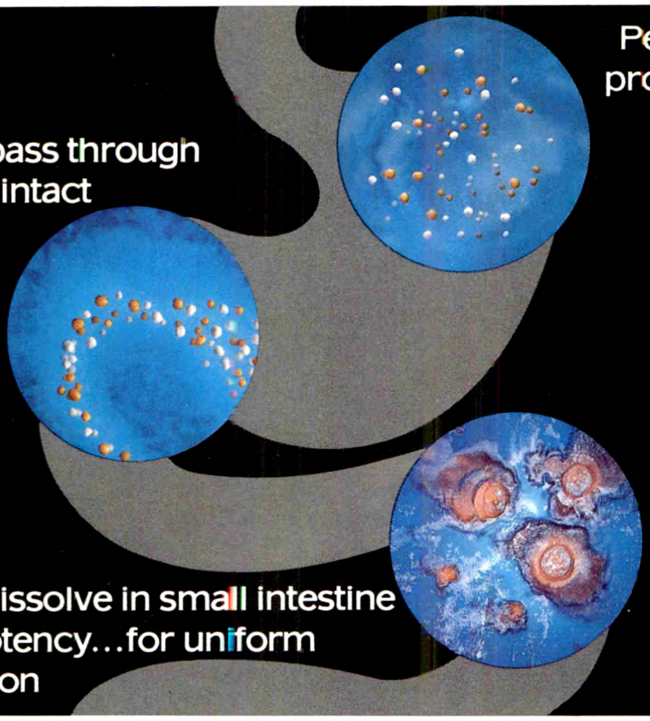

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Please see next page for brief summary of prescribing information.

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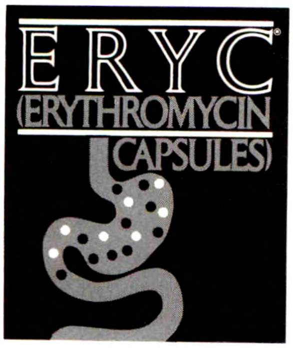

ERYC® (erythromycin capsules, USP)
Before prescribing, please see full prescribing information. A Brief Summary follows:

INDICATIONS AND USAGE: ERYC is indicated in children and adults for the treatment of the following conditions: Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes* (group A beta hemolytic streptococci); *Streptococcus pneumoniae (Diplococcus pneumoniae); Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since not all strains of *H influenzae* are susceptible at the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* (group A beta hemolytic streptococci); *Streptococcus pneumoniae (Diplococcus pneumoniae)*.

Respiratory tract infections due to *Mycoplasma pneumoniae* (Eaton's agent).

Pertussis (whooping cough) caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria — As an adjunct to antitoxin in infections due to *Corynebacterium diphtheriae*, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma — In the treatment of infections due to *Corynebacterium minutissimum*.

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Infections due to *Listeria monocytogenes*.

Skin and soft tissue infections of mild to moderate severity caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (Resistant staphylococci may emerge during treatment.)

Primary syphilis caused by *Treponema pallidum*. Erythromycin (oral forms only) is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy. The use of erythromycin for the treatment of *in utero* syphilis is not recommended (See CLINICAL PHARMACOLOGY in full prescribing information).

Legionnaires' disease caused by *Legionella pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Therapy with erythromycin should be monitored by bacteriological studies and by clinical response (See CLINICAL PHARMACOLOGY — Microbiology in full prescribing information).

Injectable benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. When oral medication is preferred for treatment of the above conditions, penicillin G, V, or erythromycin are alternate drugs of choice.

Although no controlled clinical efficacy trials have been conducted, erythromycin has been suggested by the American Heart Association and the American Dental Association for use in a regimen for prophylaxis against bacterial endocarditis in patients allergic to penicillin who have congenital and/or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract. (Erythromycin is not suitable prior to genitourinary surgery where the organisms likely to lead to bacteremia are gram-negative bacilli or the enterococcal group of streptococci.)

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint 1977 statement of the American Heart Association and the American Dental Association.

CONTRAINDICATION: ERYC is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNING: There have been a few reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin ethylsuccinate, base, and stearate products.

PRECAUTIONS: Caution should be exercised when erythromycin is administered to patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and WARNING in full prescribing information).

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Pregnancy Category B — Reproduction studies have been performed in rats, mice and rabbits using erythromycin and its various salts and esters, at doses which were several times multiples of the usual human dose. No evidence of impaired fertility or harm to the fetus that appeared related to erythromycin was reported in these studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of ERYC on labor and delivery is unknown.

Nursing Mothers — Erythromycin is excreted in milk (see CLINICAL PHARMACOLOGY in full prescribing information).

Pediatric Use — See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS: The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatic dysfunction and/or abnormal liver function test results may occur (see WARNING).

Mild allergic reactions such as rashes with or without pruritus, urticaria, bullous fixed eruptions, and eczema have been reported with erythromycin. Serious allergic reactions, including anaphylaxis have been reported.

A few cases of transient deafness have been reported with high doses of erythromycin.

DOSAGE AND ADMINISTRATION: Optimum and uniform serum levels of erythromycin are obtained when ERYC Capsules are administered one hour before meals or in the fasting state.

Adults: The usual dose is 250 mg every 6 hours taken one hour before meals. If twice-a-day dosage is desired, the recommended dose is 500 mg every 12 hours. Dosage may be increased up to 4 grams per day, according to the severity of infection. Twice-a-day dosing is not recommended when doses larger than 1 gram daily are administered.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30 to 50 mg/kg/day in divided doses. For the treatment of more severe infections, this dose may be doubled.

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VOL. 92 MARCH-APRIL 1983 NO. 2

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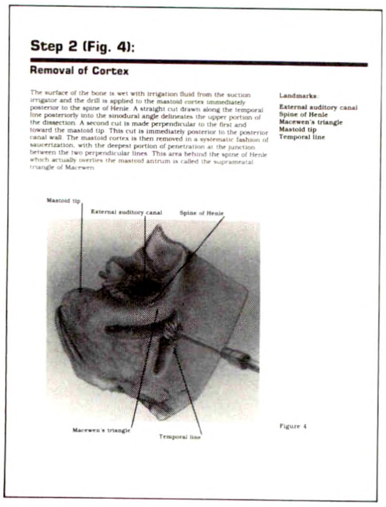

Step 2 (Fig. 4):

Removal of Cortex

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Landmarks:

External auditory canal
Spine of Henle
Macewen's triangle
Mastoid tip
Temporal line

Figure 4

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A161

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University of Michigan Medical School
Malcolm D. Graham, MD, Course Director

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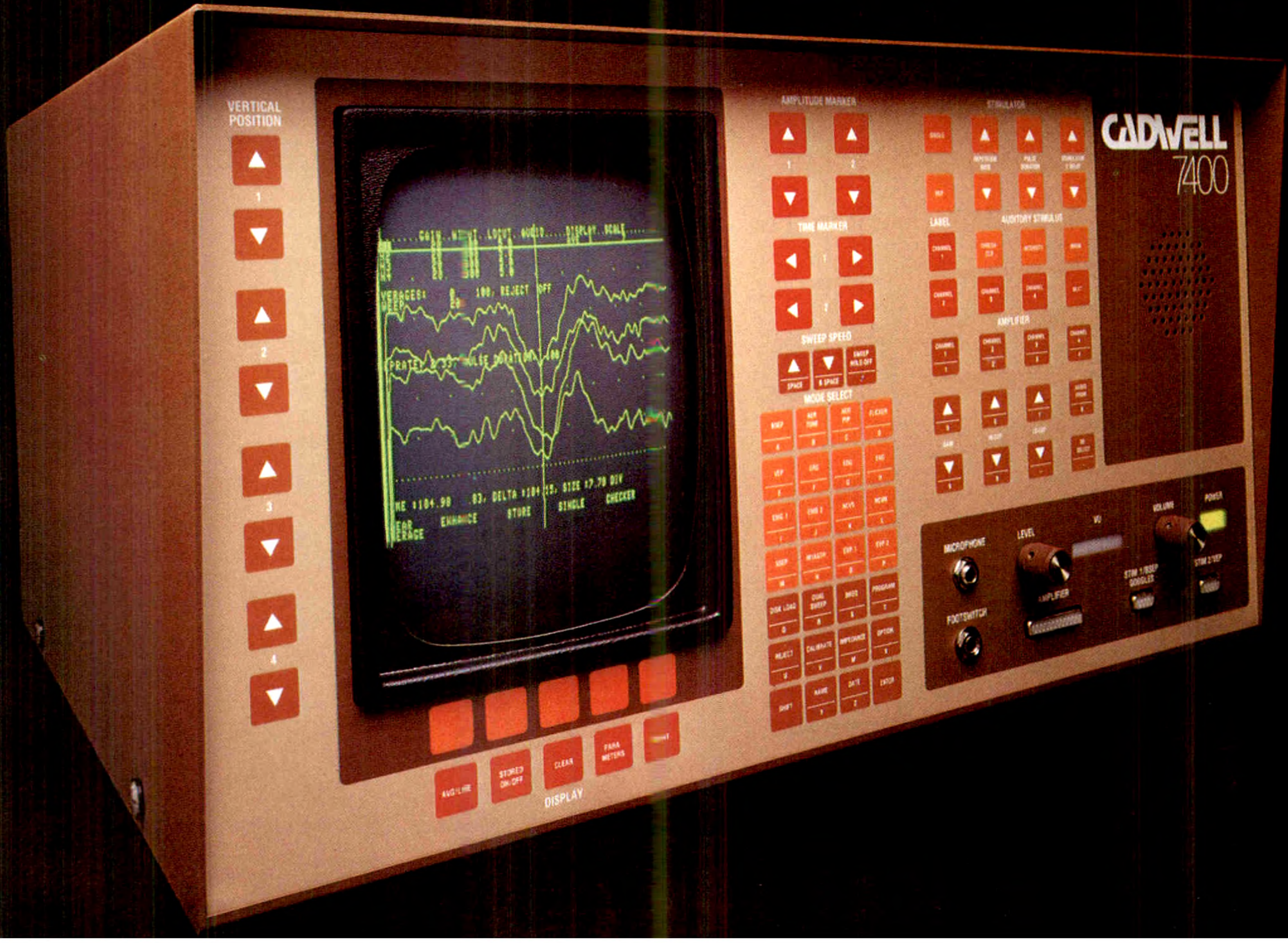

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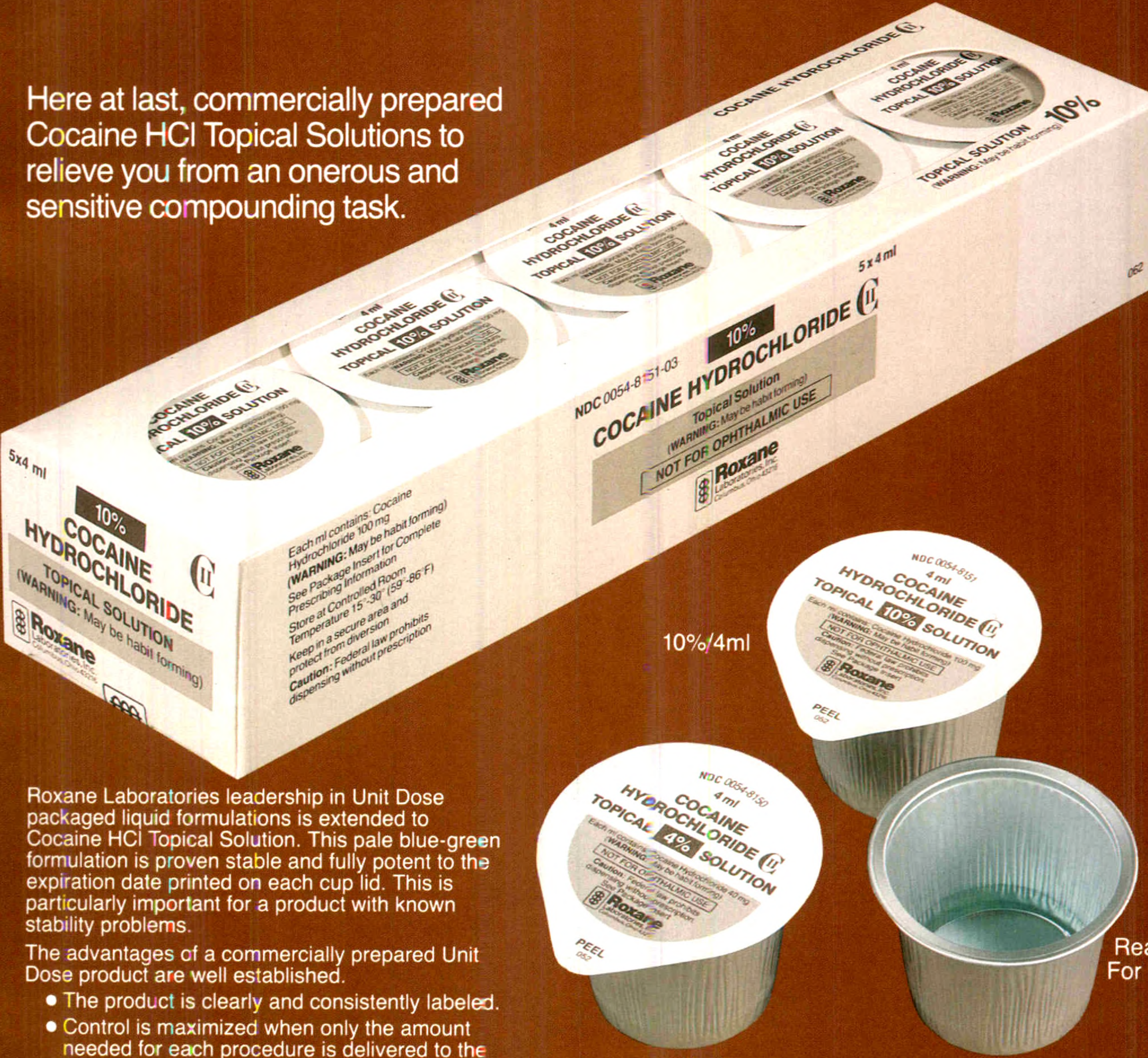

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COCAINE HYDROCHLORIDE TOPICAL SOLUTION

C II

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Will antihistamine/decongestant therapy merely replace one set of symptoms with another?

The symptoms of rhinitis may be replaced by **drowsiness**

The symptoms of rhinitis may be replaced by **CNS excitation**

The symptoms of rhinitis may be replaced by **rebound congestion**

"...When effectiveness of or tolerance to conventional treatment is unsatisfactory."[1]

[1] Nasalide brief summary of full prescribing information

Nasalide®

(flunisolide)

Compare Nasalide to antihistamines/decongestants

	NASALIDE (flunisolide)	ANTIHISTAMINES	ORAL DECONGESTANTS	NASAL DECONGESTANTS
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CNS excitation			✗	
Rebound congestion				✗

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Propylene glycol vehicle	✓		
Usual dosage*	**B.I.D.**	T.I.D.†	T.I.D.†

Nasalide offers effective therapy that's well tolerated by most patients.

Most frequent side effect is mild, transient nasal irritation or stinging (usually lasting only a few seconds).

See Adverse Reactions section of brief summary of full prescribing information.

*Dosage may be increased or decreased depending on severity of symptoms.

†Usual dosage range for beclomethasone is b.i.d. to q.i.d.

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nasal solution 0.025%

Brief Summary

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Improvement is usually apparent within a few days after starting Nasalide but may take as long as 2 weeks in some patients. Although systemic effects are minimal at recommended doses, Nasalide should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. Nasalide should not be used in the presence of untreated localized infection involving nasal mucosa.

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Warnings: Patients transferred from systemic steroid therapy to Nasalide should be monitored to avoid acute adrenal insufficiency in response to stress. Since some patients may experience symptoms of withdrawal, attention must be given to patients previously treated for prolonged periods with systemic corticosteroids, particularly those with associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of symptoms. Nasalide should be used with caution in patients on alternate-day prednisone for any disease.

Precautions: General: Localized *Candida albicans* infections of the nose and pharynx occurred only rarely in clinical studies, but if such an infection presents, treatment with appropriate local therapy or discontinuation of Nasalide® treatment may be required.

Flunisolide is absorbed into the circulation. Systemic effects have been minimal with recommended doses but larger doses should be avoided since excessive doses may suppress hypothalamic-pituitary-adrenal function.

Nasalide should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

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Information for Patients: Nasalide should be used as directed at the prescribed dosage. Nasal vasoconstrictors or oral antihistamines may be needed until the effects of Nasalide are fully manifested. The patient should follow the Patient Instructions carefully and should contact a physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs.

Carcinogenesis: While no evidence of carcinogenicity was found in a 22-month study in Swiss-derived mice, there was a slight increase in the incidence of pulmonary adenomas which was well within the range of spontaneous adenomas previously reported for untreated Swiss-derived mice.

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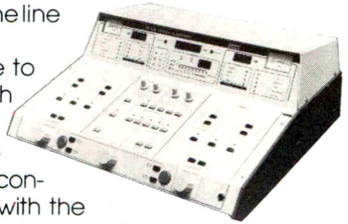

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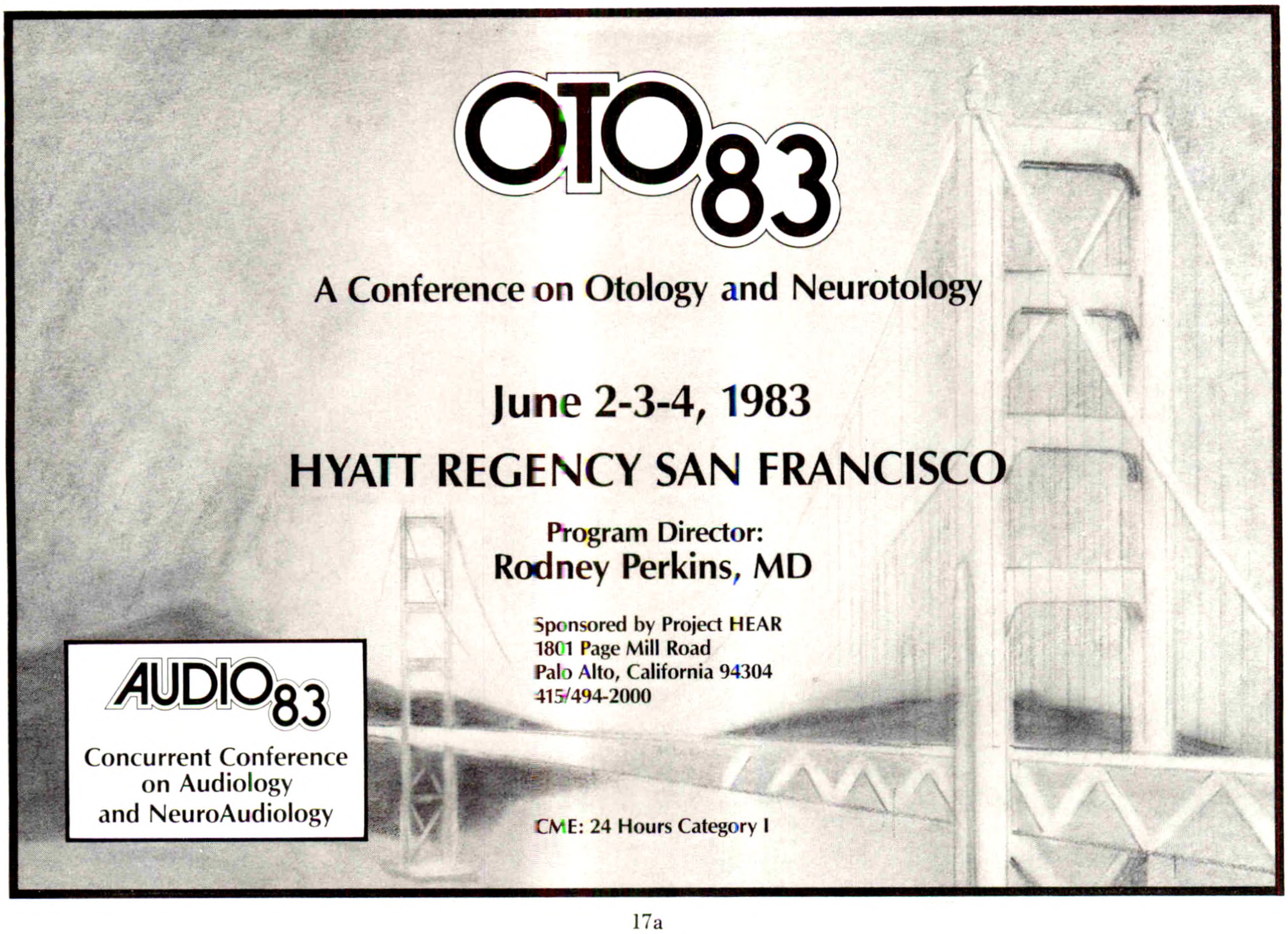

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TYPE II COLLAGEN-INDUCED AUTOIMMUNE OTOSPONGIOSIS

A PRELIMINARY REPORT

T. J. YOO, MD, PHD

K. TOMODA, MD
A. H. KANG, MD

J. M. STUART, MD
A. S. TOWNES, MD

MEMPHIS, TENNESSEE

Otospongiosis-like lesions were induced in rats by immunizing them with native type II collagen. Immunized rats had antibody responses specific for native type II collagen and developed otospongiosis-like lesions. The spongiotic lesion was characterized by numerous osteocytes and osteoblasts in the vascular spaces and by dark staining probably due to the chemical alteration of ground substances. Bone resorption and new bone formation were clearly visible. Immunofluorescence studies demonstrated deposition of immunoglobulin and complement on the bone matrix and wall within the area of spongiosis. An antibody-mediated etiopathogenesis was suspected.

Otosclerosis is a poorly understood pathological condition which causes hearing loss by affecting the otic capsules of the labyrinth and the stapes. Characteristic histopathologic changes of otosclerosis have been described in fetuses and in very young children as well as in adults of all ages. Although genetic and basic histologic patterns have been identified in otosclerosis, there is no agreement as to its etiology or precise pathogenesis.[1]

In this communication we described an experimental model of otospongiosis-like lesion in rats

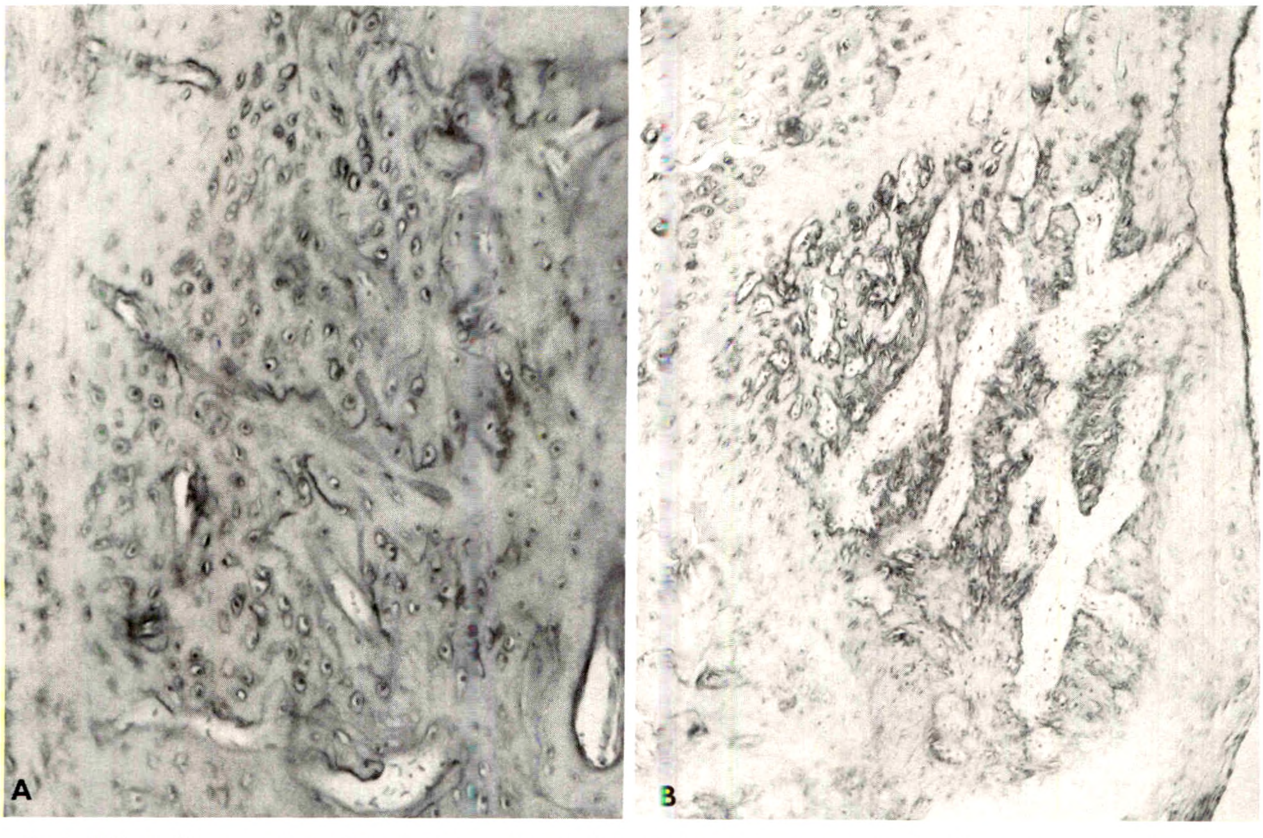

Fig 1. A) Normal bone structure of anterior border of external meatus bone near tympanic annulus. There are some vascular channels and lacunae within tissue. (x118) B) Spongiotic change at same region in rat with otospongiosis. Numerous osteocytes and osteoblasts are seen in vascular spaces of lesion. There is no defined boundary between lesion and normal bone. (x71)

From the Department of Medicine, University of Tennessee Center for the Health Sciences and VA Medical Center, Memphis.

REPRINTS — T. J. Yoo, MD, PhD, Department of Medicine, University of Tennessee Center for the Health Sciences, 956 Court Avenue, Memphis, TN 38163.

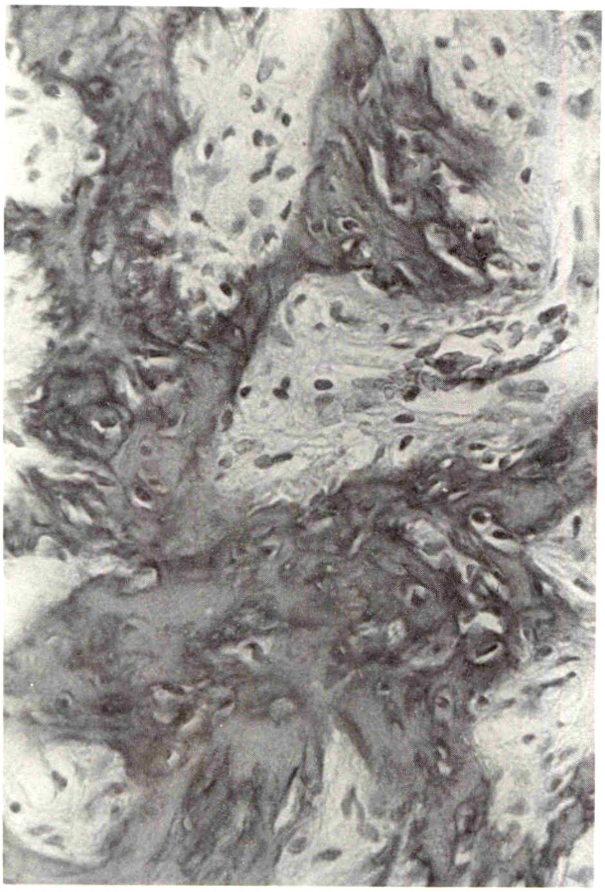

Fig 2. Higher magnification of same lesion in rat with otospongiosis (Fig. 1). Otospongiotic bone is characterized by dark staining due to alteration of chemical ground substance. Vascular spaces are wide and contain fibrous tissues. Large number of fibroblasts and osteoblasts are seen. Bone absorption and new bone formation are visible. (x672)

caused by immunization with native type II collagen. Immunized rats developed spongiotic changes in the external meatal bone near the tympanic annulus and in the middle layer of the cochlear capsule. We propose that these changes are the result of collagen autoimmunity in this animal model and may shed some new light on the possible pathogenesis of human otosclerosis.

METHODS

Inbred Lewis and outbred Wistar rats weighing 100 to 125 g were used. Rats were immunized with type I or type II bovine collagen. Pepsin-extracted collagen was prepared from skin or cartilage as previously described.[2] It was found to be pure by amino acid analysis, protein electrophoresis, and uronic acid analysis. Rats received 100 μg of collagen in 0.1 ml of 0.01 N acetic acid in incomplete Freund's adjuvant in the foot pads and were boosted one week later by another in the tail subcutaneously. Sera were collected and antibody titers were assayed by an ELISA method.[3] Animals were killed after one month and the temporal bones dissected en bloc, immersed in 10% neutral formalin, imbedded in paraffin, sectioned, and stained with hematoxylin and eosin (H and E). For the immunofluorescence studies[4] they were fixed with ethanol, decalcified with EDTA, and paraffin-imbedded before sectioning. Fluorescent-labeled rabbit antirat C3 and antirat immunoglobulin (Ig) were used to localize the deposition of antibody and complement. For control, normal rat temporal bones were used. In addition to a direct method, we also utilized an indirect method. Sections were reacted first with goat antirat IgG antisera or goat antirat C3 antisera and then with fluorescent-labeled rabbit antigoat IgG. For control, normal goat serum was reacted before reacting with fluorescent-labeled rabbit antigoat IgG.

RESULTS

Spongiotic changes were observed in the anterior border of the external meatus bone near the tympanic annulus of the type II collagen-immunized rat. No lesions were found in the rats immunized with type I collagen. In normal rats this area consists of woven and lamellar bone (Fig 1A). In type II collagen-immunized rats there were spongiotic vascular lesions characterized by numerous osteocytes and osteoblasts (dark staining was probably due to chemical alteration of ground substance) and wider vascular spaces with fibrosis (Fig 1B). Bone resorption and new bone formation were clearly visible (Fig 2). These distinctive pathological features resembled the spongification of bone which is seen in human otosclerosis. Figure 3A shows the early stage of spongification in the same part of the bone. The higher magnification in the same area (Fig 3B) shows dark staining in a large blood vessel and surrounding bone of the vascular channels and lacunae; the stain changed to dark blue due to altered chemical composition of the intercellular ground substance. This looks like the "blue mantle" seen in the early stage of human otosclerosis. Figure 4 shows boundary areas between diseased and normal bone histologically characterized by an increase in the number of osteoblasts and osteocytes, by its dark blue staining.

The early lesion of spongiotic change was observed in the middle layer of the cochlear capsule (Fig 5A). Figure 5B shows the higher magnification of the blood vessel in the cochlear capsule. Macrophages and osteoclastic cells invaded the widely vascular space and eroded perivascular bone. Surrounding interstitial bone was acellular, nonviable, and contained degenerated lacunae. However, spongiotic changes were not clearly recognized in the oval window and other areas.

Immunofluorescence studies demonstrated that the fluorescent substances were deposited on the bone matrix and vessel wall within the area of spongiosis, which was separated with a defined boundary from other normal bone. There were no fluorescent substances in the adjacent bone or in the temporal bone of control animals (Fig 6A). The temporal bones of rats with collagen-immunized spongiosis were further characterized by a strong deposition of green fluorescent substances on the enchondral layer of the otic capsule (Fig 6B,C). In normal rats, there were no fluorescent substances on the same area. In the sections stained with H and E there were no differences between the control and collagen-immunized rats except the thin blue staining on the surface of the lacunae and canaliculae. In addition, the walls of the vascular channels were

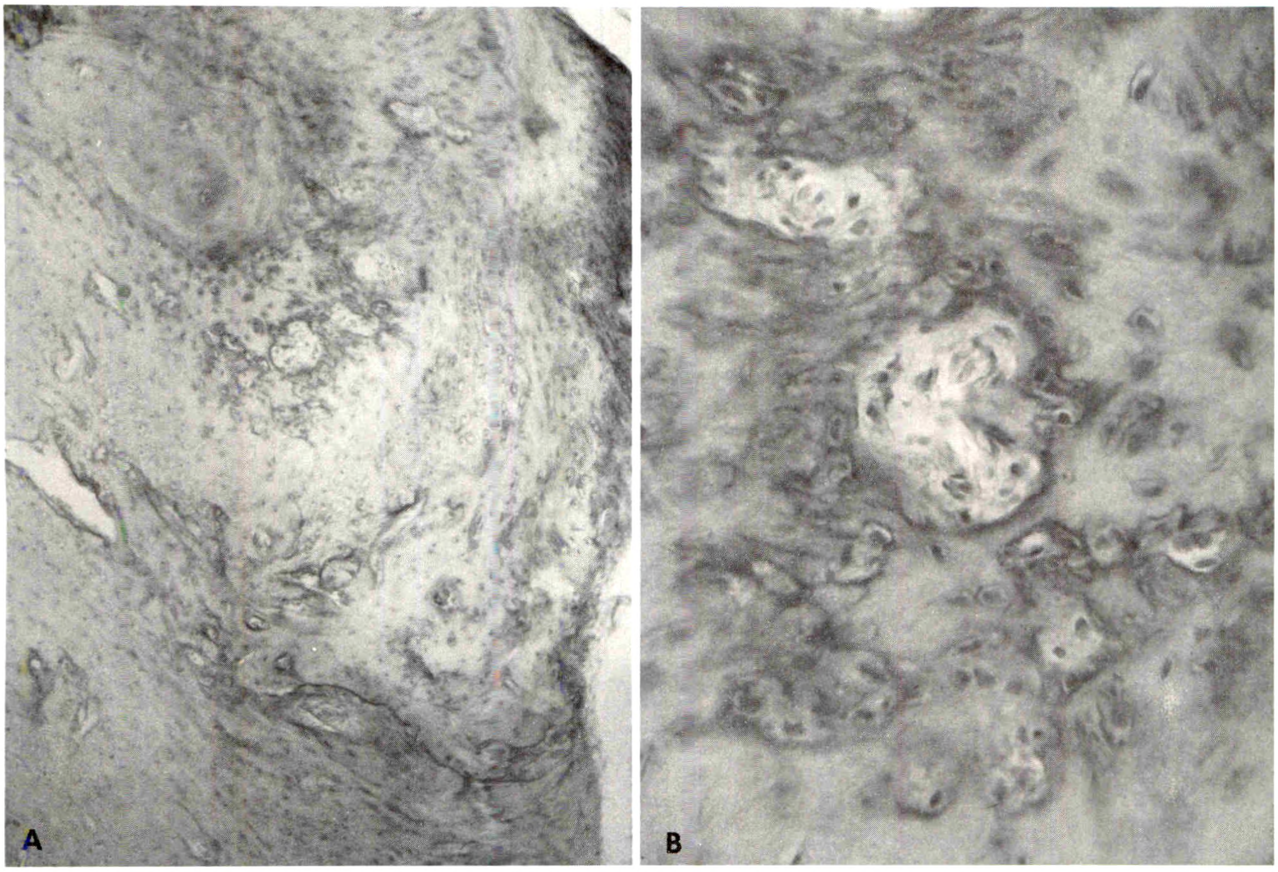

Fig 3. A) Early stage of spongification seen in anterior border of external meatal bone near tympanic annulus in type II collagen-immunized rat (x18). B) Higher magnification in same area, showing dark staining in blood vessel and surrounding bone of vascular channels and lacunae as shown in Fig 2. This feature looks like "blue mantle" as seen in early stage of human otosclerosis. (x178)

slightly more prominent in immunized as compared to normal rats. The Table shows a comparison of otospongiotic changes in normal rats and type II collagen-immunized rats.

Ossicular maxillary joints of immunized and control rats had normal histology in both H and E and immunofluorescence sections, whereas in the immunofluorescence sections, the bone tissue of ossicles from the type II collagen-immunized rats had a deposition of green fluorescent substances around lacunae, canaliculae, and vascular channels.

Antibodies to type II collagen were detected in these rats by ELISA. Mean absorbance of a 1:1000 dilution of sera from ten experimental rats was 1.096 ± 0.086 compared to 0.083 ± 0.006 for unimmunized controls. Similar results were obtained in type I collagen-immunized rats; these animals had antibodies against type I collagen. The preimmunization antibody level of experimental animals was the same as that of the unimmunized control animals. Preincubation of the sera with 50 μg/ml of type I collagen showed minimum inhibition while preincubation with 50 μg/ml of type II collagen reduced the absorbance to control levels. We had previously shown that antisera raised in rats against bovine type II collagen extensively cross-reacts with

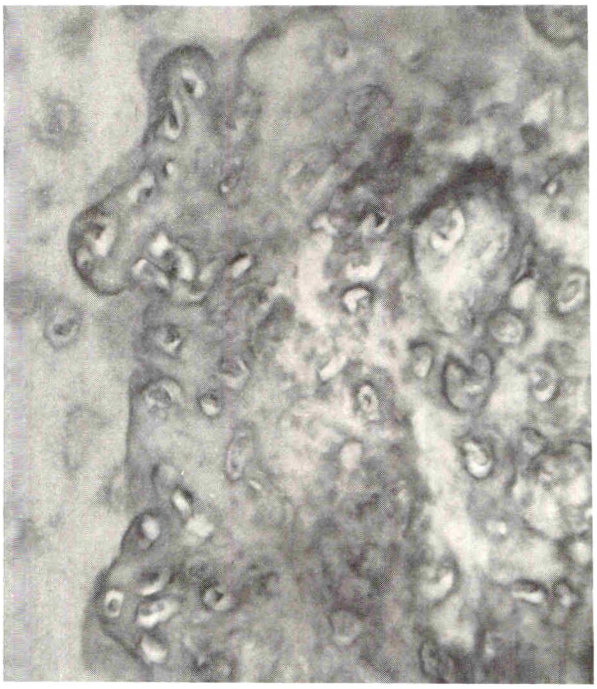

Fig 4. Another case in type II collagen-immunized rat showing boundary area between diseased and normal bone in anterior border of external meatal bone near tympanic annulus histologically characterized by increase in number and activity of osteoblasts and osteocytes, and also by its dark staining as shown in Fig 2. (x168)

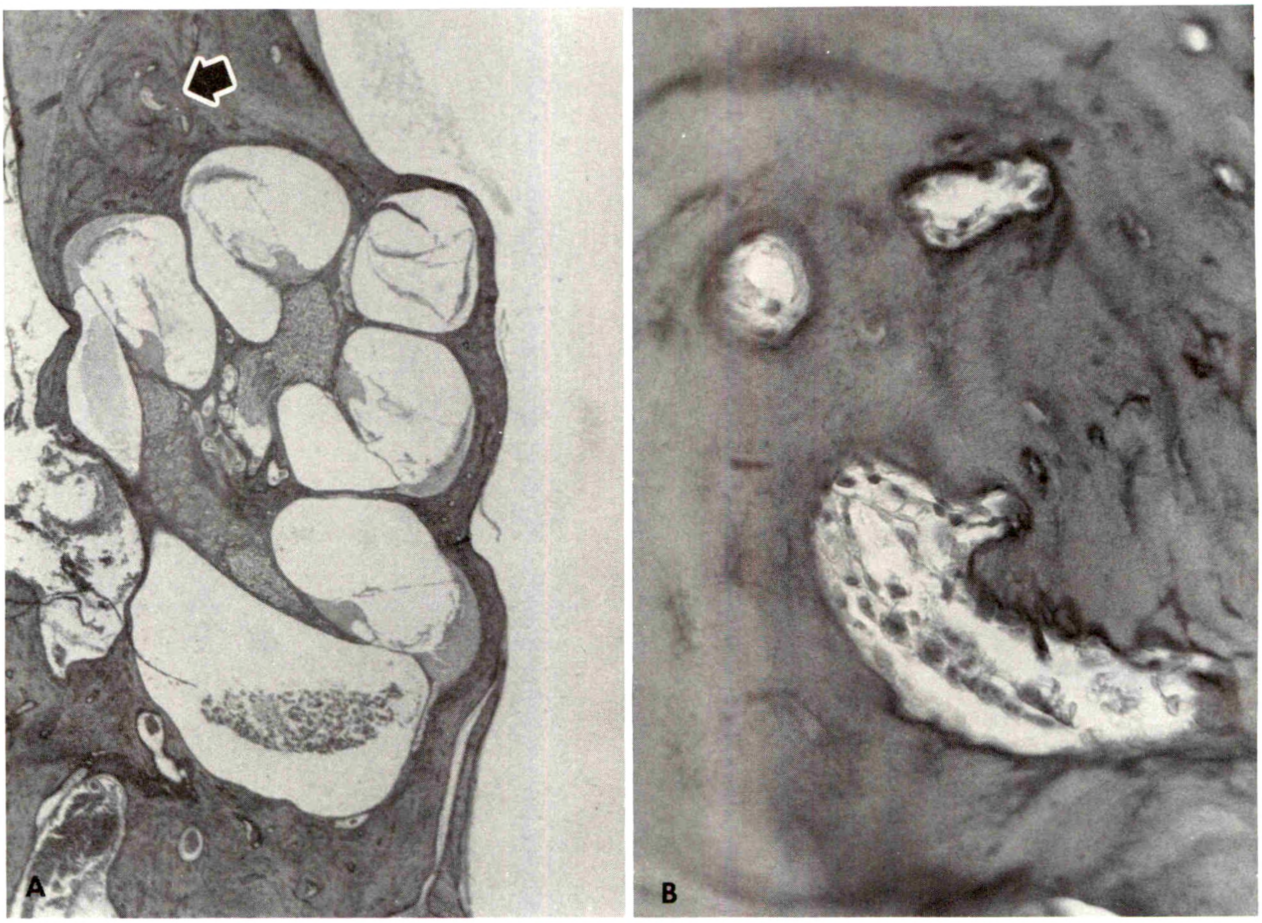

Fig 5. A) Early lesion of spongiotic change observed in middle layer of cochlear capsule (arrow) (x16). B) Higher magnification of blood vessel in cochlear capsule. Macrophages and osteoclastic cells invaded widely dilated vascular space and eroded perivascular bone. Surrounding interstitial bone are acellular and nonviable containing degenerated lacunae. (x158)

rat type II collagen, hence these antibodies suggest "autoimmunity."[2,5,6]

DISCUSSION

The primary lesion of human otosclerosis occurs in the otic capsule. The earliest change is actually an otospongiosis-softening or "spongiosis" due to increased vascularity and resorption of bone.[1] The major etiologic theories of otosclerosis deal with the presence of unstable rests of embryonic cartilage and histiocytes within the capsule and fissula, and it is thought that enzymatic activity from the histiocytes results in otospongiotic changes.[7-9]

Up to now, enzyme studies on otospongiosis indicate that enzymes are responsible for the destruction of bony tissue. It is possible that these changes are caused by the inflammatory cells recruited to the immune reaction site.

SPONGIOTIC CHANGE IN NORMAL AND COLLAGEN-IMMUNIZED RAT

	Normal (12 Ears)		*Collagen-Immunized Rat (25 Ears)*	
	(−)	(+)	(−)	(+)
Spongiosis	11	1	5	20
Osteogenic cell reaction	10	2	4	21
Vascular spaces	12		5	20
Altered intercellular ground substance	11	1	5	20

Collagen is a major structural component of connective tissue[10,11] and hypersensitivity to type II collagen associated with arthritis in rats,[2,5,6,12] mice (Stuart JM, Townes AS, Kang AH; unpublished data), and humans,[13] chondritis of the ear lobe in rats,[4] and relapsing polychondritis in humans.[14] In this communication we report for the first time an animal model showing that autoimmunity to type II collagen can cause "otospongiosis-like" changes in the ear.

Histological similarities exist between our experimentally produced lesion and human otosclerosis, but the lesion is less prominent in the labyrinthine capsule, and no lesion is observed in the stapedio-vestibular joint. However, these regions are coated with antibody as detected by immunofluorescence. The pathology may not have been advanced enough to be apparent in this particular area. However, the immunofluorescent deposits are found in both the enchondral layer of the otic capsules and the anterior border of the external meatus bone near the tympanic annulus.

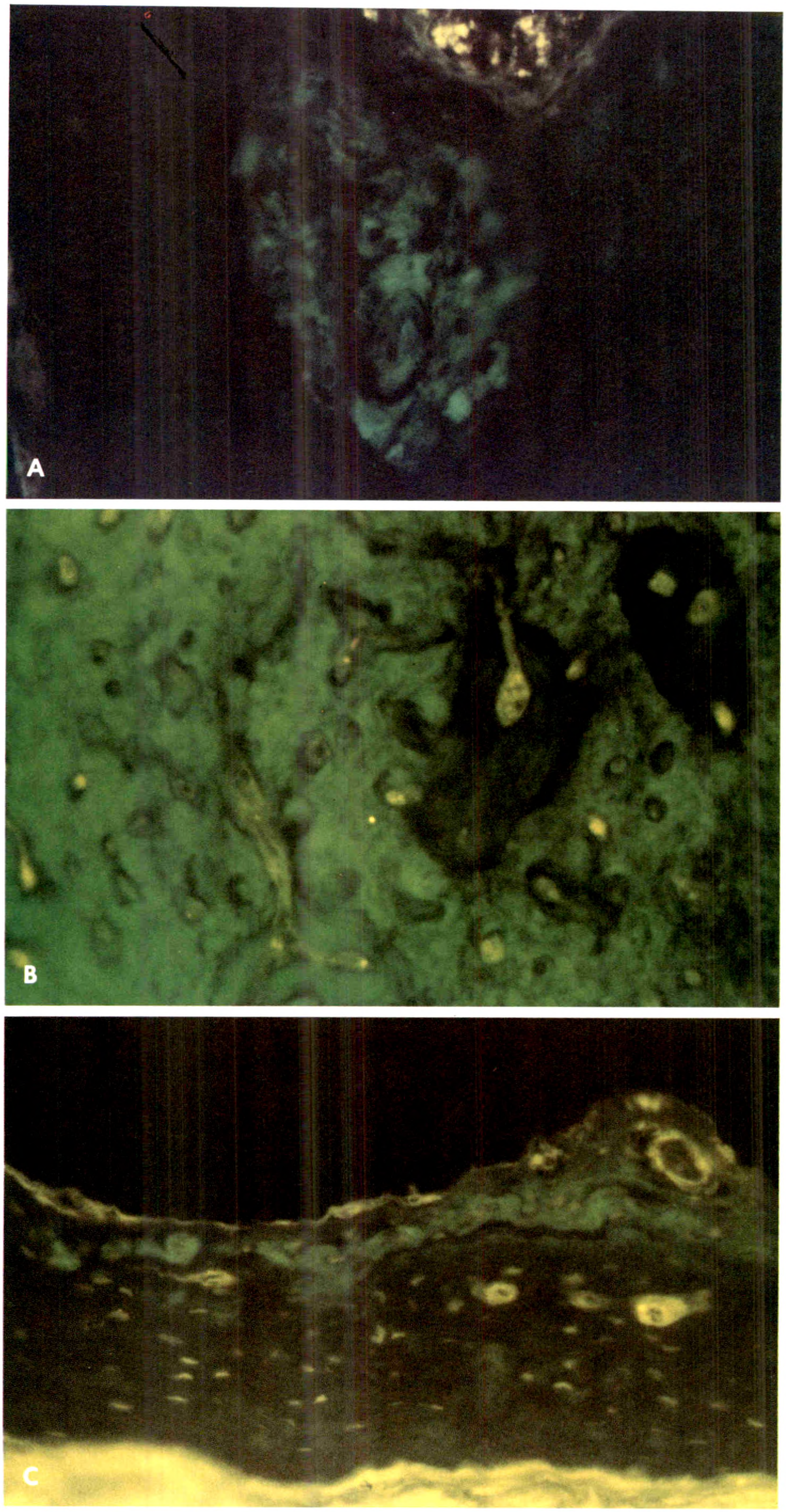

Fig 6. A) Immunofluorescence staining demonstrating green fluorescent substance responding to rat-IgG and C3 deposited in spongiotic lesion located with defined boundary from adjacent bone in same part of external meatal bone (antirat IgG antisera, x71). B) Strong deposition of green fluorescence observed on enchondral layer of otic capsule in type II collagen-immunized rat. Positive reaction to antirat IgG and C3 appeared in the area of globuli interossei (antirat IgG, antisera x2556). C) Enchondral layer of cochlear capsule also showing positive reaction against rat-C3 in type II collagen-imunized rat (antirat C3, antisera x2045).

We are not sure why the spongiotic changes occurred in this area except that here four-minute ossification centers of membrane bone fuse in the early stages of temporal bone development. Also the anterior border is the last area in the normal fixation to other parts of the temporal bone. Thus, it might be feasible that this anterior border of the tympanic annulus could be more susceptible to an immune injury. It would be attractive to hypothesize that cartilage remnants exist in this area although we do not have any experimental evidence so far to support this thesis.

Whether or not autoimmunity to collagen is involved in human ear disease is not known, however, this animal model provides an opportunity to investigate human otosclerosis with this concept. Preliminary studies performed in our laboratory also suggest that some patients with otosclerosis have collagen autoimmunity.[15] On this basis, we would like to propose that the spongiosis may be initiated by collagen autoimmunity. Immune reactions directed against the cartilage rests could explain the presence of histocytes as well as the pathophysiology and clinical picture of otosclerosis. Thus this animal model may provide a new avenue of research and may be useful in defining the pathogenesis of human otosclerosis.

REFERENCES

1. Lindsay JR. Otosclerosis. In: Paparella MM, Schumrick DA, eds. Otolaryngology. Vol 2. Philadelphia: WB Saunders, 1980:1617-43.

2. Trentham DE, Townes AS, Kang AH. Autoimmunity to type II collagen: an experimental model of arthritis. J Exp Med 1977; 146:857-68.

3. Cremer MA, Pitcock JA, Stuart JM, Kang AH, Townes AS. Auricular chondritis in rats: an experimental model of relapsing polychondritis induced with type II collagen. J Exp Med 1981; 154:535-40.

4. Sainte-Marie G. A paraffin embedding technique for studies employing immunofluorescence. J Histochem Cytochem 1962; 10:250-6.

5. Stuart JM, Cremer MA, Kang AH, Townes AS. Collagen-induced arthritis in rats; evaluation of early immunologic events. Arthritis Rheum 1979; 22:1344-51.

6. Trentham DE, Townes AS, Kang AH, David JR. Humoral and cellular sensitivity to collagen in type II collagen-induced arthritis in rats. J Clin Invest 1978; 61:89-96.

7. Bretlau P, Causse J, Jorgensen BM, Chevance LG. Histiocytic activity in the otosclerotic bone. Arch Klin Exp Ohren Nasen Kehlkopfheilkd 1971; 198:301-16.

8. Causse J, Shambaugh GE, Chevance LG, Bretlau P. Cochlear otospongiosis etiology diagnosis and therapeutic implications. Adv Otorhinolaryngol 1977; 22:43-56.

9. Causse J, Chevance LG, Bretlau P, Jorgensen ME, Uriel J, Berges J. Enzymatic concept of otospongiosis and cochlear otospongiosis. Clin Otolaryngol 1977; 2:23-32.

10. Timpl R. Immunological studies on collagen. In: Ramechandraw GN, Reddi AH, eds. Biochemistry of collagen. New York: Plenum Publishing Co, 1976:319-75.

11. Timpl R, Von der Mark K, Von der Mark H. Immunochemistry and immunohistology of collagen. In: Viidik A, Vuust J, eds. Biology of collagen. New York: Academic Press, 1980: 211-22.

12. Cremer MA, Stuart JM, Townes AS, Kang AH. Collagen-induced polyarthritis in rats: a study of native type II collagen for adjuvant activity. J Immunol 1980; 124:2912-8.

13. Stuart JM, Postlewaite AE, Townes AS, Kang AH. Cell mediated immunity to collagen and collagen α chains in rheumatoid arthritis and other rheumatic diseases. Am J Med 1980; 69:13-8.

14. Pearson CM. Relapsing polychondritis in clinical immunology. In: Parker CW, ed. Philadelphia: WB Saunders Co, 1980:774-83.

15. Yoo TJ, Stuart JM, Kang AH, Townes AS, Tomoda K, Dixit S. Type II collagen autoimmunity in otosclerosis and Meniere's disease. Science 1982; 217:1153-5.

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CHEMODECTOMA OF THE CHEEK

A CASE REPORT

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The first case of a chemodectoma of the cheek is presented and the histopathology reviewed. Chemodectomas of the head and neck can be difficult to diagnose, with angiography remaining the single most useful aid to determining both location and diagnosis. Surgery is the treatment of choice, and prognosis depends not only on the extent of the tumor but also its predilection for malignant behavior.

INTRODUCTION

Chemodectomas or nonchromaffin paragangliomas are a histologically similar group of tumors that arise from chemoreceptive tissues throughout the body. These tumors are commonly found in the head and neck as glomus jugulare tumors, glomus vagale tumors, or glomus tympanicus tumors. In fact, they are the most common neoplasm of the middle ear and are second in occurrence only to acoustic neuromas within the temporal bone.[1]

Unusually located chemodectomas in the head and neck region are also being reported in increasing numbers;[2-7] however, the present case is the first reported case of a chemodectoma of the cheek.

CASE REPORT

The patient is a 26-year-old male whose only symptom was a vague discomfort in his right cheek for approximately one year. Associated with this discomfort was an intermittent biting of his right cheek, which he attributed to a dental problem. A dental consultation led to a biopsy of a submucosal mass in his right buccal area, and a tentative diagnosis of hemangiopericytoma was obtained. The patient was referred to the Medical Center Hospital of Vermont for further evaluation and treatment.

On bimanual palpation, the mass involved the middle and superior portion of the right cheek. Intraorally, the mass extended submucosally to the gingival buccal sulcus superiorly and to the retromolar trigone posteriorly. The inferior gingival buccal sulcus was free of disease. The mass appeared to be stuck to the masseter muscle with possible involvement of the parotid gland. There was no dental pathology evident, and all cranial nerves functioned normally. There was no palpable adenopathy. The remainder of his ENT examination was normal.

Tomograms of the base of the skull and maxilla revealed no evidence of bony erosion in these areas. A right parotid sialogram was normal; however, a right common and external carotid arteriogram (Fig. 1A) revealed a moderately vascular mass supplied by hypertrophied branches of the internal maxillary artery. Vascular encasement was not present. The mass appeared to be localized to the right cheek and did not extend posteriorly into the soft tissues of the oropharynx or nasopharynx. The CAT scan (Fig. 1B) revealed a soft tissue mass involving the soft tissues of the cheek with extension limited to the anterior portion of the masseter muscle.

In June 1980, the patient underwent superficial parotidectomy for exposure of the facial nerve fibers and of the tumor. The mass was located exactly as expected from the physical examination and radiographic findings. To assure adequate margins, it was removed en bloc with the involved portion of the masseter muscle, the buccal fat pad, and with the adjacent oral mucosa. The mucosal defect could be closed for the most part by direct approximation; however, at the conclusion of the procedure there was still approximately a 2 cm residual defect, which healed of its own accord over the ensuing weeks.

On gross pathological examination, the mass measured approximately 4 cm in diameter. It was firm, completely encapsulated, and mottled brown-white in color on its cut surface.

Microscopically, the tumor contained epithelioid cells arranged in variations of organoid, gyraform, and trabecular patterns (Fig. 2A). The cells contained pale, faintly eosinophilic cytoplasm with large nuclei (Fig. 2B). There was minimal pleomorphism. The stroma was highly vascular with numerous large vessels being surrounded by cell clusters in a perithelious manner (Fig. 2C). On the basis of the endocrinoid appearance and highly vascular stroma, a diagnosis of chemodectoma was made.

The patient experienced an unremarkable postoperative course and has no evidence of persistent or recurrent disease two years after surgery.

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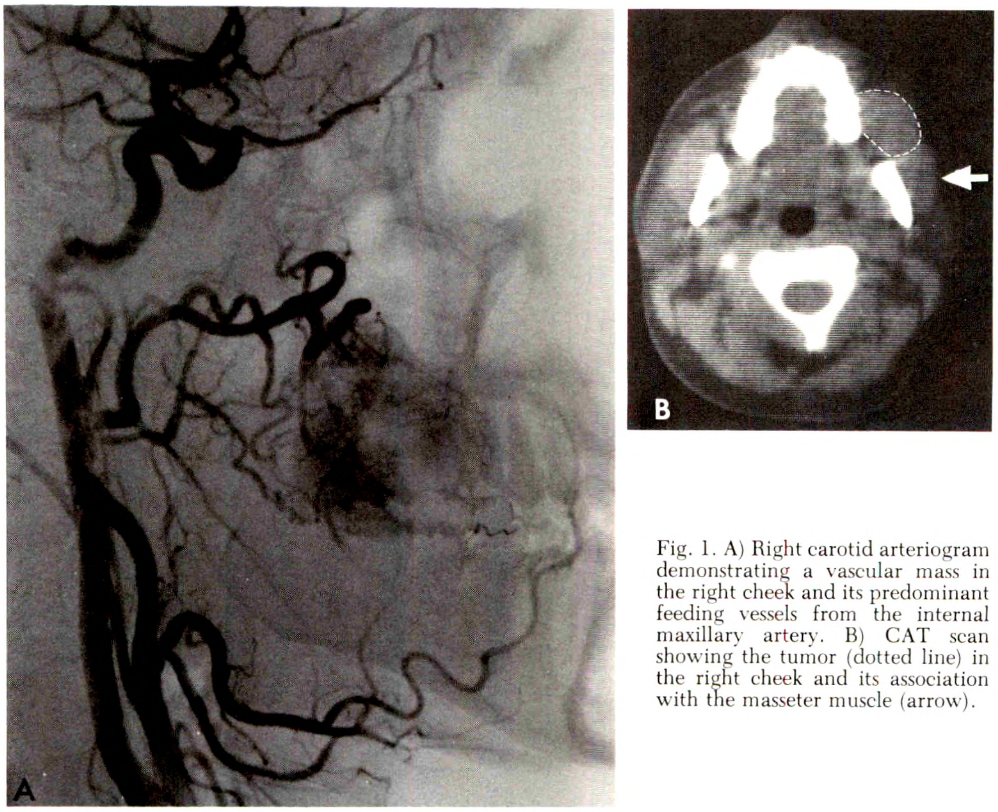

Fig. 1. A) Right carotid arteriogram demonstrating a vascular mass in the right cheek and its predominant feeding vessels from the internal maxillary artery. B) CAT scan showing the tumor (dotted line) in the right cheek and its association with the masseter muscle (arrow).

DISCUSSION

In the middle of the 18th century, Haller[8] described a soft tissue irregular, ovoid, pale structure on the medial wall of the common carotid artery at its bifurcation. He originally thought the structure to be a sympathetic ganglion and so termed it "ganglion minitum." Subsequently, this structure has become recognized as the carotid bulb and regarded as a paraganglion. The chemoreceptor tissue which comprises it has been found to be widely dispersed throughout the body.

On gross histological examination, most paragangliomas are partially encapsulated, firm, and tan on cut-section. Trabecular fibrosis and focal hemorrhage are occasionally noted.

Microscopically, the tumors consist of sheets or nests of epithelioid (chief) cells arranged in distinct clusters (*Zellballen*) and cell cords. These arrangements are usually separated by prominent capillary networks, and the tumor itself is generally encapsulated by fibrous stroma with interdigitating fibrosepti.

The chief cell is the predominant cell and varies from ovoid to polyhedral in configuration. It generally contains a moderate amount of pale eosinophilic granular cytoplasm with vesicular nuclei. There is variable pleomorphism, and mitotic figures are exceedingly rare. Catecholamine-like granules in the chief cells have been demonstrated by ultrastructural studies, and some paragangliomas have been associated with symptoms due to excess catecholamine secretion, such as paroxysmal hypertension.[9-11]

The chief cells are believed to belong to a larger family of cells termed amine, precursor, uptake, and decarboxylation (APUD) cells. These cells arise from the neural crest and give origin to several tissues other than the chemoreceptor cells of chemodectomas. These tissues are then capable of developing their own specific tumors, which belong to the larger family called "APUDomas"; for example, chromaffin cells giving rise to pheochromocytomas, thyroid C cells giving rise to medullary carcinoma, GI endocrine cells giving rise to intestinal carcinoid, etc.[12]

Chemodectomas typically follow a slowly progressive, insidious clinical course with symptoms varying with the location of the tumor. The correct clinical diagnosis of a chemodectoma is difficult to make, especially in the more unlikely areas. The most informative diagnostic procedure, as in the present case, is selective angiography. It is also possible to perform preoperative embolization during the diagnostic angiography if any prominent vessels are identified. A CAT scan with renograffin enhancement may serve equally well to demonstrate the vascular nature and extent of tumor, but would not delineate any of the feeding vessels. Incisional biopsy is ideal in reaching a preoperative di-

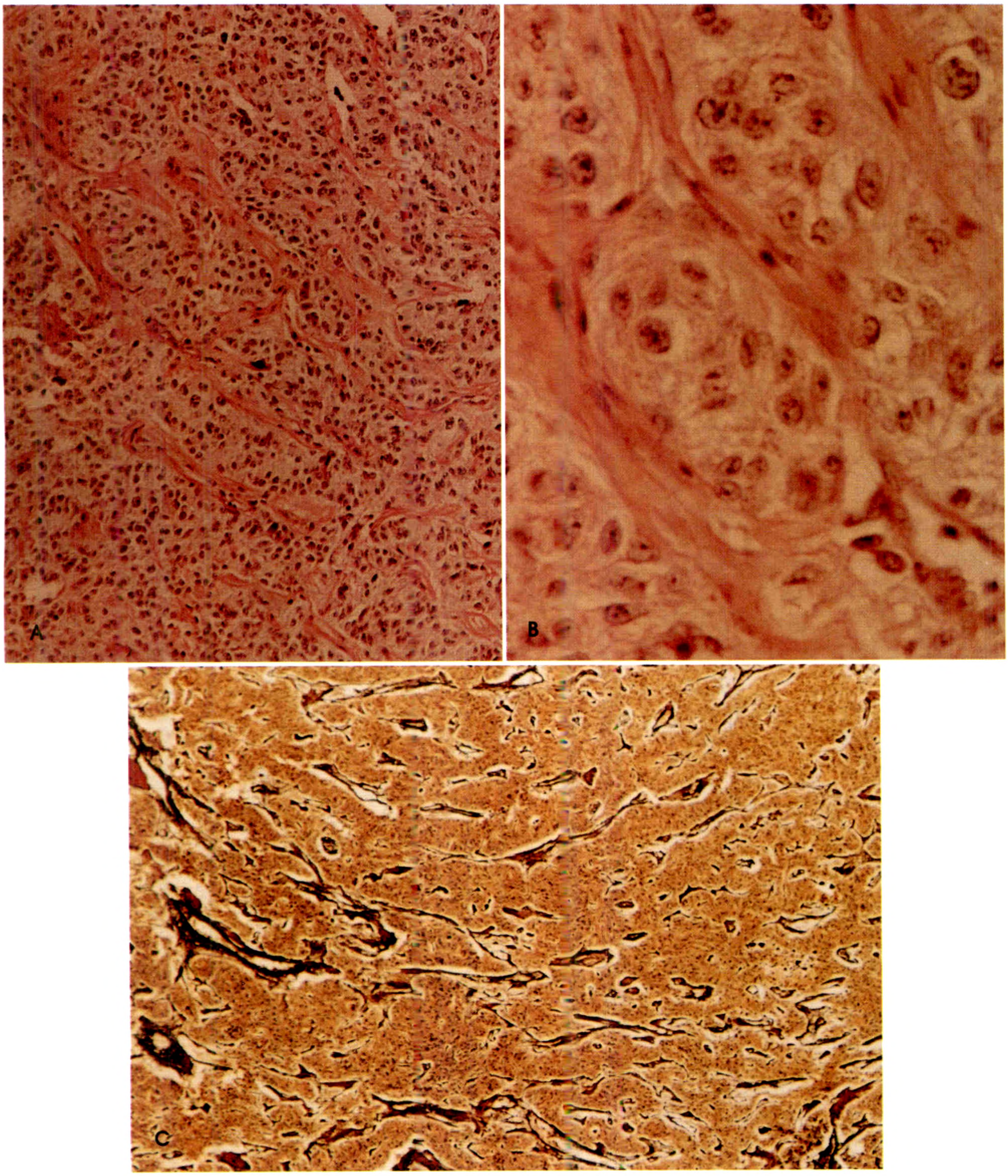

Fig. 2. A) Photomicrograph of the tumor illustrating its organoid and trabecular arrangements of epithelioid cells (x100). B) Photomicrograph showing the large nuclei and pale eosinophilic cytoplasm of the chief cells (x400). C) Photomicrograph demonstrating the tumor's highly vascular stroma (x40 -reticulum stain).

agnosis but is not always recommended because of its potential for inducing uncontrollable hemorrhage.

Surgery remains the treatment of choice. If major feeding vessels are present, their ligation or embolization prior to excision of the tumor can result in a significantly diminished operative blood loss. Radiation therapy is reserved primarily for unresectable lesions. Its major effect appears to be on the vascular and fibrous elements of the tumor, rather than to directly destroy tumor cells.[13-15]

Although these tumors are usually benign, malignant potential has been demonstrated with metastases being noted to the lung, cervical and mediastinal lymph nodes, heart, liver, and bone.[6,7,9] Lack et al[7] noted that malignant paragangliomas exhibited a combination of two or more of the following histologic features: central necrosis of the *Zellballen*, invasion of the vascular spaces, and the presence of mitotic figures. However, Batsakis[11] feels that there is no correlation between the histologic appearance of these tumors and their biologic behavior.

A relationship between malignant behavior of chemodectomas and their site of origin has been noted. Among the more commonly located paragangliomas, the vagal body tumors (16%) have the highest incidence of metastases.[16] However, when all locations in the head and neck are considered, laryngeal tumors have been associated most frequently with a malignant course (approximately 25%).[17] Therefore, prognosis may depend on both the extent of the primary lesion and the location, with its associated tendency for malignant behavior.

REFERENCES

1. Spector GJ, Sobol S. Surgery for glomus tumors of the skull base. Otolaryngology Head Neck Surg 1980; 88:524-30.

2. Andrews AH Jr. Glomus tumors (nonchromaffin paraganglioma) of the larynx: case report. Ann Otol Rhinol Laryngol 1955; 64:1034-6.

3. Zeman MS. Carotid body tumor of the trachea. Ann Otol Rhinol Laryngol 1956; 65:960-2.

4. Schall LA. An endolaryngeal approach for certain benign lesions of the larynx. Trans Am Laryngol Assoc 1959; 80:36-47.

5. Baxter JD. Glomus tumor (chemodectoma) of the larynx. Ann Otol Rhinol Laryngol 1965; 74:813-20.

6. Rossenwasser H. Glomus jugulare tumors, VI. Follow-up of cases. Arch Otolaryngol 1968; 88:35-40.

7. Lack EE, Cubilla AL, Woodruff JM. Paragangliomas of the head and neck region. Hum Pathol 1979; 10:191-218.

8. Haller A. Elementa physiologiae corporis humani. Lausanne 1757-1763; 4:256-7.

9. Oberman HA, Holtz F, Sheffer LA, Magielski JE. Chemodectomas (nonchromaffin paragangliomas) of the head and neck. Cancer 1968; 21:838-50.

10. Levit SA, Sheps SG, Espinosa RE, ReMine WH, Harrison EG Jr. Catecholamine-secreting paraganglioma of glomus jugulare region resembling pheochomocytoma. N Eng J Med 1969; 281:805-11.

11. Batsakis J. Chemodectomas of the head and neck. In: Batsakis J, ed. Tumors of the head and neck. Baltimore: Williams & Wilkins Co, 1974:286-8.

12. Tischler AS. Neuroendocrine neoplasms and their cells of origin. N Eng J Med 1977; 296:919-25.

13. Capps FCW. Chemodectoma of tumor of the glomus jugulare and tympanic bodies. Arch Otolaryngol 1958; 67:556-9.

14. Brackmann DE, House WF, Terry R. Glomus jugulare tumors: effects of irradiation. Trans Am Acad Ophthalmol Otolaryngol 1972; 76:1423-31.

15. Spector GJ, Maisel RH, Ogura JH. Glomus jugulare tumors II. A clinicopathologic analysis of the effect of radiotherapy. Ann Otol Rhinol Laryngol 1974; 83:26-32.

16. Kahn LB. Vagal body tumor (nonchromaffin paraganglioma, chemodectoma, and carotid body-like tumor) with cervical node metastasis and familial association. Cancer 1976; 38:2367-77.

17. Gallivan MVE, Chun B, Rowden G, Lack EE. Laryngeal paraganglioma. Case report with ultrastructural analysis. Am J Surg Pathol 1979; 3:85-92.

TENTH ANNIVERSARY CONFERENCE ON COCHLEAR IMPLANTS: AN INTERNATIONAL SYMPOSIUM

The Tenth Anniversary Conference of the International Symposium on Cochlear Implants will be held June 22-24, 1983, at the University of California in San Francisco. For further information write or call: Extended Programs in Medical Education, University of California School of Medicine, Room 569-U, Third and Parnassus, San Francisco, CA 94143; (415) 666-4251.

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ENDOLYMPHATIC SAC SURGERY FOR MENIÈRE'S DISEASE

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An endolymphatic-mastoid Silastic shunt procedure was performed in 122 cases of Menière's disease having a mean follow-up period of three years. In accordance with American Academy of Ophthalmology and Otolaryngology 1972 criteria, there were 43% class A, 20% class B, 21% class C, and 17% class D results. Analysis of 35 recent cases having a mean follow-up period of nine months revealed 57% class A, 25% class B, 9% class C, and 9% class D results. Sixteen percent of the patients who experienced classes A, B or C results complained of other fluctuating symptoms which were not relieved by surgery. Moreover, three new cases of otolithic crisis were found in the postoperative group. Seven of ten patients who experienced a class A or B result had either a recrudescence of their vertigo or a significant decrement in hearing in response to a postoperative salt-loading test. It is concluded that the surgical success rate decreases with time and that the procedure appears to alter the symptom complex but does not cure Menière's disease.

INTRODUCTION

In 1861, Menière[1] described the symptom complex of episodic vertigo, fluctuating progressive hearing loss, and tinnitus. Guild[2] postulated the longitudinal endolymphatic flow theory and provided supportive evidence when he injected dye into the basal turn of the cochlea of a guinea pig and recovered it in the endolymphatic sac. Recently, Kimura et al[3] put forth strong evidence in support of the longitudinal flow theory. The action of the endolymphatic sac was considered to be resorptive. Naftalin and Harrison[4] and Lawrence et al[5] proposed the radial endolymphatic flow theory. It appears that the dark cells in the labyrinth have properties consistent with secretory function[6] and that the outer sulcus cells of the cochlea may have a resorptive function.[7]

In 1938 Hallpike and Cairns[8] and Yamakawa[9] independently demonstrated endolymphatic hydrops in the human temporal bone. Lindsay and Von Schulthess[10] showed cochlear hydrops without vestibular disease in 1958. Naito,[11] Kimura and Schuknecht[12] and Schuknecht et al[13] produced histologic evidence of endolymphatic hydrops in the guinea pig and the cat by endolymphatic sac obliteration. In 1921 Portmann[14] produced vestibular disturbances in fish by sealing the endolymphatic sac. Five years later he suggested drainage of the endolymphatic sac for the relief of vertigo.[15] Since then, the endolymphatic sac has been decompressed, neovascularized, shunted to the subarachnoid space or mastoid cavity and catherized with various prostheses, including Silastic or Gelfoam sheeting, tubes, sponges, and unidirectional valves for the relief of vertigo and preservation of hearing in Menière's disease.[16-29]

The purpose of this report is to evaluate the long-term effects of endolymphatic-mastoid shunting with Silastic sheeting on the course of Menière's disease in 122 cases (120 patients). The study is divided into four parts:

1. Evaluation of the long-term relief of vertigo and conservation of hearing;
2. Comparison of the long-term results to the results noted in a subgroup of 35 more recently operated patients;
3. Analysis of associated symptoms which have developed in the long-term postoperative patient group; and
4. Analysis of the response to a postoperative salt-loading test in ten patients who experienced a favorable surgical result.

MATERIALS AND METHODS

Evaluation, Medical Treatment, and Indications for Surgery. Approximately 300 patients with episodic vertigo, tinnitus and a fluctuating hearing loss are seen annually at Barnes Hospital, St. Louis, and allied hospitals. Each patient undergoes 1) an audiometric profile, including pure-tone, speech and impedance audiometry and a provocative glycerol test with or without salt-loading;[30-32] 2) electronystagmography, including bithermal caloric stimulation, and gaze, positioning and positional testing; 3) internal auditory canal polytomography or high resolution computerized tomography with and without contrast enhancement; 4) neurological consultation; 5) hematological testing for syphilis and diabetes mellitus; and 6) an otologic, audiometric and electronystagmographic evaluation during an attack.

Patients diagnosed as having Menière's disease are placed on a medical regimen for at least three months. Our present regimen includes an antiemetic, a daily diuretic with potassium supplementation, and a 2 g sodium diet. In addition, the patient is urged to curtail the use of tobacco and alcohol.

Approximately 5% of our patients with Menière's disease are eventually recommended for an endolymphatic-mastoid shunt procedure. Criteria for surgical intervention clearly tend to incorporate either patients who have signs associated with a favorable surgical result but are significantly disabled, or those whose only other alternative would be a labyrinthectomy (Table 1). Patients who have bilateral disease in association with marginally service-

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TABLE 1. CRITERIA USED IN CONSIDERING PATIENTS FOR ENDOLYMPHATIC-MASTOID SHUNT SURGERY

Objective documentation of fluctuating hearing loss of more than 1 yr
Objective documentation of episodic vertigo of more than 1 yr
Voluntary statement by patient regarding significant disability
Documentation by physician statement or self-maintained diary of incidence, severity and duration of attacks covering a period greater than 3 mo
Evidence of a significant accident precipitated by a vertiginous attack (rare)
Positive glycerol test based on AAOO (1972) criteria
Rapidly progressive hearing loss with or without intractable vertigo (rare)
Medical failure
Bilateral disease with marginally serviceable hearing
Candidacy for a labyrinthectomy

able hearing (50 dB speech reception threshold [SRT] and/or a 50% speech discrimination score [SDS]) may not be candidates for streptomycin therapy due to their borderline cochlear reserve. Tinnitus and aural fullness are not considered as criteria for surgery.

Surgical Population. From July 1971 to August 1979, 120 patients having at least a 12-month history of Menière's disease underwent 122 standardized endolymphatic-mastoid shunts. The average age was 44.6 years with a range of 12 to 77 years. There were 77 females and 43 males. The average duration of symptoms prior to surgery was 32 months with a range of 12 to 120 months. One of the 120 patients had osteopetrosis, and another suffered an otolithic crisis prior to surgery. Eight patients were noted to have a negative glycerol test. Six of these patients were candidates for a labyrinthectomy and the remaining two patients had posttraumatic perilymphatic fistulae with secondary hydrops.

Operative Technique. A complete, simple mastoidectomy is performed initially. The posterior semicircular canal is exposed but not blue-lined. The endolymphatic sac is exposed and its lateral or mastoid wall opened widely. The endolymphatic duct is then probed bluntly for a short distance along its course medial to the posterior semicircular canal. The duct is then cannulated with a wedge-shaped sheet of Silastic which is stabilized by the imbrication of the lateral wall of the sac. The mastoid cavity is neither drained nor packed with Gelfoam. The wound is thoroughly irrigated and closed.

Data Acquisition and Length of Follow-up. Each patient was seen at one week, six months and annually following surgery. Data was obtained from an assessment of 1) the patient's postoperative history and self-maintained diary; 2) results of a self-administered questionnaire; and 3) results of an annual audiogram and bithermal caloric nystagmogram. The results were tabulated in accordance with AAOO 1972 criteria[33] (Table 2) with the "best" preoperative audiogram used as the baseline for the classification of the postoperative hearing result as suggested by Arenberg et al.[34]

Patients having less than one year of follow-up were excluded from the determinate, or long-term group. Postoperative data at the 1-year interval was obtained on all of the cases. Over 1-year follow-up data were collected on 97% of the cases. The average length of follow-up was 3 years with a range of 1-8 years.

For comparative purposes, data was collated on the 35 cases performed during the 2-year period immediately preceding the August 1979 cutoff. To avoid confusion, these cases are collectively referred to as the short-term subgroup in the remainder of this report. The subgroup included 13 cases with less than 1-year follow-up, which, by definition, excluded them from the determinant group. The follow-up period of the short-term subgroup ranged from 6 to 18 months, with an average of 9 months.

TABLE 2. AAOO (1972) CRITERIA FOR REPORTING RESULTS IN THE TREATMENT OF MENIERE'S DISEASE

AAOO (1972) Class	*Criteria*
A	Vertigo relieved; hearing improved (15 dB SRT or 15% SDS gain)
B	Vertigo relieved; hearing unchanged
C	Vertigo relieved; hearing worse (15 dB SRT or 15% SDS loss)
D	Vertigo not controlled

RESULTS

Long-Term Results. Results of a study of the long-term group are summarized in Table 3. In 52 cases (43%) vertigo was eliminated and hearing significantly improved relative to the "best" preoperative audiogram. Hearing was stabilized and vertigo relieved in 24 cases (20%). Thus, vertigo was improved and hearing either stabilized or improved in 63% of the cases. A relief of vertigo with a decrease in hearing was noted in 25 cases (21%). Hence, 83% of the entire group experienced a relief or amelioration of their vertigo.

The audiometric profile did not change significantly in most of the 21 patients in whom vertigo was not controlled. Eight of these patients subsequently required a transcanal labyrinthectomy for relief of vertigo. One of these patients demonstrated a persistent ataxia, but did not complain of vertigo, postoperatively.

Electronystagmographic results were not altered significantly by surgery. On bithermal caloric stimulation during an asymptomatic state, 76% of the cases exhibited a canal weakness, 14% demonstrated a directional preponderance and 10% were noted to have a normal response.

Although not considered to be criteria for predicting surgical success, tinnitus and the sensation of fullness were eliminated in 13% and 26% of the cases, respectively. The latter usually occurred in those who experienced the best postoperative results.

Two of the six patients who were otherwise candidates for a labyrinthectomy had a class A result, including serviceable hearing. One patient in this

TABLE 3. LONG-TERM RESULTS OF ENDOLYMPHATIC-MASTOID SHUNTING IN PATIENTS WITH MENIERE'S DISEASE

AAOO (1972) Class	*Number of Cases*	*Percent of Total Population N = 122*
A	52*	43
B	24	20
C	25†	21
D	21*	17

*One patient with secondary hydrops.

†One patient with osteopetrosis.

TABLE 4. SHORT-TERM RESULTS OF ENDOLYMPHATIC-MASTOID SHUNTING IN PATIENTS WITH MENIÈRE'S DISEASE

AAOO (1972) Class	*Number of Cases*	*Percent of Total Population N = 35*
A	20	57
B	9	25
C	3	9
D	3	9

group experienced a class B result, and the others exhibited a class D result.

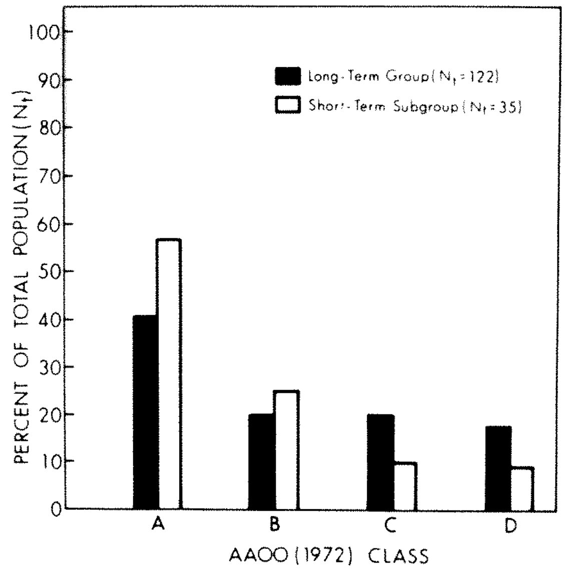
The endolymphatic sac could not be delineated in four patients. Although they were excluded from the sample population of 120 patients, it is interesting to note that 1 of the 4 patients enjoyed a class B result, another had a class C result, and the 2 remaining patients experienced a class D result.

There was no evidence of a postoperative dead ear, conductive hearing loss, facial nerve deficit, semicircular canal fistulae, wound infection, intracranial complication or death in the entire group of patients.

Comparison of Short- and Long-Term Results. We have noted that some patients who had a favorable response to surgery (class A or B) at the 1-year interval experienced either a decrement in hearing or a recurrence of vertigo. In an effort to assess the magnitude of this disturbing trend, we examined the results of the previously defined short-term subgroup, a summary of which is given in Table 4. Vertigo was relieved in 91% of the cases, while hearing was either stabilized or improved in 82% of the subgroup. These results are significantly better ($p < 0.01$) than those of the long-term group, a graphic comparison of which is given in the Figure.

Associated Symptoms. A review of the postoperative histories and diaries of those patients whose vertigo was relieved on a long-term basis revealed other disturbing findings. Sixteen of the 101 class A, B and C patients complained of an episodic unsteadiness, lightheadedness or a mild ataxia associated with vegetative symptoms, such as nausea, vomiting or diaphoresis. They denied symptoms suggestive of true vertigo. Moreover, these same patients related a fluctuating tinnitus or a sensation of fullness and loudness intolerance. We could find only a slight decrease (less than 5 dB) in the SRT in the follow-up audiograms of these patients. Six of the 16 patients characterized their unsteadiness as being positionally dependent; however, we were unable to document the presence of a benign paroxysmal postural vertigo on electronystagmography.

Three patients with a class C result developed a postoperative otolithic crisis (usually associated with end-stage Menière's disease and characterized by momentary loss of control of the extensor muscle group without a change in the level of consciousness) which was not present before surgery.



Comparison of long- and short-term results of endolymphatic mastoid shunting. N_t - Total no. of patients.

The remainder of the patients experienced a definite improvement in their symptoms; however, few considered themselves completely cured. Many indicated that they continued to experience unpleasant, poorly described sensations (eg, sensitivity to constant motion) and several complained of an aggravation of such discomfort in association with an increased salt intake.

Provocative Salt-Loading Test. In order to formally assess the effects of an increased salt intake, nine patients (ten operated ears) who had a class A or B result were willingly subjected to a postoperative salt-loading test. All of the patients exhibited a positive glycerol test in the affected ear preoperatively. Each patient was given a daily 3 g salt supplement to a regular diet over a 2-week period. Pure-tone and speech audiograms were obtained at the 1-week, 2-week and 1-month interval. If the patient experienced an adverse response, a full audiologic and electronystagmographic evaluation was performed immediately, salt-loading discontinued, and diuretic therapy started. None of the patients required hospitalization as a consequence of the test.

A test was considered positive if either vertigo was induced or a hearing decrement greater than 15 dB SRT or 15% SDS was verified.

Seven of the patients exhibited a positive response (2 class A and 5 class B patients). In general, each complained initially of an increased sensation of fullness in the affected ear; this was soon accompanied by an increase in the preloading level of tinnitus. The first audiometric change noted was diminution of the SDS; this was followed by a decrease in either the SRT or pure-tone average.

Loudness recruitment was generally accentuated in these cases. All seven of these patients experienced an exacerbation of their unsteadiness. Three complained of transient episodes of true vertigo, one of whom manifested a spontaneous nystagmus which was documented by electronystagmography.

At the completion of the salt-loading test, two patients were relegated to a lower AAOO (1972) class as a result of a permanent decrease in hearing. The remaining patients maintained their original postoperative status. The electronystagmographic profiles were not permanently altered by the test in any of the patients.

DISCUSSION

Menière's disease is one of protean manifestations. The duration, severity, and variability of the vertiginous and auditory attacks in a patient cannot be prognosticated on the basis of the previous pattern of the attacks in that individual. A scientific evaluation of a specific therapeutic measure in a disease of unknown origin with an unpredictable behavioral pattern is most difficult. The problem can be demonstrated by considering two other therapeutic approaches — pharmacological and physical.

Medical protocols used in the treatment of Menière's disease are numerous.[35] We demonstrated in a retrospective study of 35-50 months' duration that vitamins, antihistamines, histamine and histamine analogs, and oral vasodilators were of no benefit.[36] Guilford[37] noted that all forms of medical therapy resulted in approximately 66-70% improvement or relief; other authors[18] felt that this data may reflect the natural course and/or spontaneous resolution of Menière's disease. We currently use salt restriction, long-term oral diuretics and antimetics, a regimen proposed originally (with slight modification) by Furstenberg et al[38] in 1934.

A similar problem exists when one evaluated the efficacy of various physical modalities in the treatment of vertigo. The application of ultrasound to the horizontal semicircular canal for the relief of vertigo was first suggested by Kroejci.[39] James,[40] in reporting on the results of 331 patients treated with ultrasound, claimed a 90% cessation of and 10% improvement in vertigo. In addition, he noted a 13% improvement and 40% stabilization of hearing at the same level of power. Pennington and Stevens[41] obtained relief of vertigo in 80% of their patients treated with ultrasound. Moreover, 90% of the patients experienced an improvement or stabilization of their hearing.

A review of the results of cryosurgery on either the horizontal or posterior semicircular canals indicates that vertigo is relieved and hearing either maintained or improved in about 70% of the patients. In addition, tinnitus and fullness are relieved in 50% of the patients. House[42] performed cryosurgery of the promontory in 80 patients and obtained relief of vertigo with stabilized or improved hearing in 70%; relief of vertigo and decreased hearing in 9% of the patients; no response to the therapy in 11%; and brief responses but recurrence of symptoms within six months in 9% of the patients. Wolfson and Cutt[43] applied cryosurgery to the horizontal canal in 112 patients (135 procedures) and noted a stabilization or improvement of hearing and vertigo in 79% of the patients.

Taken collectively, endolymphatic sac procedures provide relief of vertigo in 65-90% of the cases, stabilization or improvement in hearing in 65-85%, and relief of tinnitus or aural fullness in 13-50% of the cases.[17-29,44-50]

House and Owens[19] reporting on 146 patients who underwent endolymphatic-subarachnoid shunts, noted control of vertigo in 39% and improvement in hearing in 24% of the patients. Clemis and Shambaugh[17] reported relief of vertigo in 64% and a stabilization or improvement in hearing in 17% of their patients who underwent similar procedures. In a more recent study, Brackmann and Anderson[50] obtained control of vertigo in 61% and either improvement or stabilization in hearing in 52% of 125 patients who underwent endolymphatic-subarachnoid shunting; however, 36 of the patients eventually required additional surgery for control of their disease. Others have reported slightly better results with the use of endolymphatic-subarachnoid shunts.[44-46]

Results obtained with the use of an endolymphatic-mastoid Silastic shunt are similar to those noted for an endolymphatic subarachnoid shunt. For example, Arenberg and Spector[22] obtained relief of vertigo in 89% and improvement or stabilization in hearing in 78% of 20 patients having positive glycerol tests. Paparella and Hanson[23] reported control of vertigo in 82% and an improvement or stabilization of hearing in 71% of 46 patients who underwent an endolymphatic-mastoid shunt. Morrison et al[25] noted either stabilization or improvement in hearing in 94% of 263 patients who exhibited a positive glyercol test preoperatively.

Arenberg et al[21] recently reported preliminary results of endolymphatic-mastoid shunting with a unidirectional valve shunt in 78 patients. They noted that hearing improved in 54% or stabilized in 20%, and vertigo was controlled in 89% of these patients. In another study, Arenberg and Stahle[48] found that the valvular shunt outperformed the simple Silastic sheet shunt by 23% in terms of hearing improvement or stabilization and by 26% with respect to the control of vertigo at a 2-year follow-up interval. Arenberg and Stahle[49] claim that in 39 patients who had end-stage disease and were candidates for a labyrinthectomy, insertion of a unidirectional valve improved hearing in 39%, stabilized hearing in 18%, and controlled vertigo in 87% of the patients.

A comparative analysis of the results of endolymphatic sac surgery is made more difficult because of the variability in the length of follow-up associated with the reported studies. House[19] noted that over a period of 1-2 years about 25% of the patients who underwent an endolymphatic-subarachnoid shunt had a recrudescence of their vertiginous symptoms. A review of the results of the present study reveals that over a 27-month period approximately 8% of our patients experienced a recurrence of their vertigo; moreover 19% of the patients were noted to have a significant diminution of their early hearing gain. Whether this trend represents a failure of the operative technique to provide long-term shunting or alter the natural course of the disease is not known. Both House[19] and Brackmann and Anderson[50] noted an obstructive peritubular fibrosis in patients requiring revision of their endolymphatic-subarachnoid shunts. Moreover, the senior author of this study has noted a fibroproliferative response about the Silastic shunt in seven patients who required revision surgery. A direct evaluation of the long-term patency of the unidirectional valve has not been performed. However, some insight into the problems associated with this prosthesis can be gained by examining the results obtained with the use of its prototype, the Krupin valve,[51] in the treatment of neovascular glaucoma. In such cases, fluid can be observed within the lumen and a reduction of intraocular pressure can be measured to validate its efficacy. Krupin et al[51] noted that in 42 operated patients there were 11 cases of periluminal fibrosis and 2 cases of intraluminal obstruction secondary to fibrosis.

The answer to the question of whether endolymphatic sac shunting significantly alters the underlying pathology of Menière's disease remains even more obscure. None of the sac procedures in current use provide for a decompression or cannulation of the more proximal portion of the endolymphatic duct. Clemis and Valvassori[52] presented radiographic evidence of a narrowing of the endolymphatic duct in patients with Menière's disease. Clearly, a decompression or shunting of just the distal portion the endolymphatic system may not be sufficient under these circumstances. Moreover, although the pathologic process involved in the "cochlear" variant of Menière's disease is not fully understood, one would logically place the site of lesion proximal to the sac. The results of a recent histopathologic study by Kimura et al[3] lend support to this argument. Why, then, do patients who manifest signs and symptoms of such a disorder experience a favorable response to distal shunting with a unidirectional valve? Perhaps, as suggested by Schuknecht,[53] the localized trauma inherent in the procedure creates a mild inflammatory reaction that temporarily alters the underlying pathophysiology.

It may be that a decompression or distal shunt provides for only a partial decrease in the overall flow resistance. The postoperative salt-loading test described earlier represents a dynamic disturbance of a quasi-steady-state system. The fact that a number of patients with a favorable surgical result exhibited a positive response suggests a decompression that relieves the hydrops in the semisteady, postoperative state but cannot accommodate a presumed increase in the endolymphatic flow rate in the stressed state.

The fact that some patients who exhibited a favorable surgical result complained of persistent, albeit vague, fluctuating symptoms is most disturbing. Furthermore, the finding of three new cases of otolithic crisis in the postoperative group is yet another indication that the underlying pathology has not been resolved.

CONCLUSIONS

It is evident from the data presented here that endolymphatic-mastoid Silastic shunting is not a curative procedure. However, the symptom complex does appear to be altered by such surgical intervention and a significant number of patients obtain at least temporary relief from their vertiginous and auditory attacks. The physiologic basis of endolymphatic sac surgery remains somewhat obscure, and it may be possible that when the pathophysiology of Menière's disease is better understood, there will be a small, select group of patients who will require endolymphatic sac shunting as an optimal therapeutic modality.

REFERENCES

1. Meniere PM. Memoire sur de lesions de l'oreille interne dormant lieu a des symptomes des congestion cerebrale apoplectiforme. Gazette Med de Paris 1861; 16:597.

2. Guild SR. The circulation of the endolymph. Am J Anat 1927; 39:57-81.

3. Kimura RS, Schuknecht HF, Ota CY, Jones DD. Obliteration of the ductus reuniens. Acta Otolaryngol (Stockh) 1980; 89: 295-309.

4. Naftalin L, Harrison MS. Circulation of labyrinthine fluids. J Laryngol Otol 1958; 72:118-36.

5. Lawrence M, Wolsk D, Litton WB. Circulation of inner ear fluids. Ann Otol Rhinol Laryngol 1961; 70:753-76.

6. Kimura R, Lindquist PG, Wersall J. Secretory epithelial linings in the ampullae of the guinea pig labyrinth. Acta Otolaryngol (Stockh) 1964; 57:517-30.

7. Saxen A. Histological studies of endolymph secretion and resorption in the inner ear. Acta Otolaryngol (Stockh) 1951; 40: 23-31.

8. Hallpike CS, Cairns H. Observations on the pathology of Meniere's syndrome. J Laryngol Otol 1938; 53:625-54.

9. Yamakawa K. Uber die pathologische veranderungenbei einem Meniere-Kranken. Oto-Rhino-Laryngol 1938; 34:181.

10. Lindsay JR, Von Schulthess G. An unusual case of labyrinthine hydrops. Acta Otolaryngol (Stockh) 1958; 49:315-24.

11. Naito T. Clinical and pathological studies of Meniere's disease. 60th Annual Meeting of the Oto-Rhino-Laryngol Society, Tokyo, 1958.

12. Kimura RS, Schuknecht H. Membranous hydrops in the inner ear of the guinea pig after obliteration of the endolymphatic sac. Pract Oto-Rhino-Laryngol 1965; 27:343-54.

13. Schuknecht HF, Northrop C, Igarashi M. Cochlear pathology after destruction of the endolymphatic sac in the cat. Acta Otolaryngol (Stockh) 1968; 65:479-87.

14. Portmann G. Recherches sur la physiologie du sac et du canal endolymphatiques: valeur fonctionelle de l'organ endolymphatique des selaciens. C R Soc Biol 1921; 85:1070-2.

15. Portmann G. Vertigo-surgical treatment by opening the saccus endolymphaticus. Arch Otolaryngol 1927; 6:309-19.

16. Shambaugh GE Jr. Decompression of the endolymphatic sac for hydrops. Otolaryngol Clin North Am 1968; 1:607-11.

17. Clemis JD, Shambaugh GE Jr. Preliminary experiences with operations on the endolymphatic sac. Laryngoscope 1966; 76:1029-41.

18. House WF. Subarachnoid shunt for drainage of endolymphatic hydrops — a preliminary report. Laryngoscope 1962; 72: 713-29.

19. House WF. Subarachnoid shunt for drainage of endolymphatic hydrops — a report of 146 cases. Laryngoscope 1965; 75: 1547-51.

20. House WF, Owens FD. Long term results of endolymphatic subarachnoid shunt surgery in Meniere's disease. J Laryngol Otol 1973; 87:521-7.

21. Arenberg IK, Stahle J, Glasscock ME III, Shambaugh GE Jr, Newkirk JB. Endolymphatic sac valve implant surgery. Laryngoscope 1979; 89 Suppl 17.

22. Arenberg IK, Spector GJ. Endolymphatic sac surgery for hearing conservation in Meniere disease. Arch Otolaryngol 1977; 103:268-70.

23. Paparella MM, Hanson DG. Endolymphatic sac drainage for intractable vertigo (method and experiences). Laryngoscope 1976; 86:697-703.

24. Morrison AW. The surgery of vertigo: saccus drainage for idiopathic endolymphatic hydrops. J Laryngol Otol 1976; 90: 87-93.

25. Morrison AW, Moffat DA, O'Connor AF. Clinical usefulness of electrocochleography surgery in Meniere's disease: an analysis of dehydrating agents. Otolaryngol Clin North Am 1980; 13:703-21.

26. Alford BR, Cohn AM, Igarashi M. Current status of surgical decompression and drainage procedures on the endolymphatic system. Ann Otol Rhinol Laryngol 1977; 86:683-8.

27. Shambaugh GE Jr. Surgery of the endolymphatic sac. Arch Otolaryngol 1966; 83:305-15.

28. Shea JJ. Surgery of the endolymphatic sac. Otolaryngol Clin North Am 1968; 1:613-21.

29. Austin DF. The endolymphatic shunt operation. Otolaryngol Clin North Am 1968; 1:589-606.

30. Klockhoff I, Lindblom V. Endolymphatic hydrops revealed by glycerol test: preliminary report. Acta Otolaryngol (Stockh) 1966; 61:459-62.

31. Arenberg IK, Stroud MH, Spector GJ. The salt loading provocative glycerol test for early diagnosis of endolymphatic hydrops (Meniere's disease). A preliminary report. Rev Laryngol Otol Rhinol 1974; 95:709-18.

32. Swanson SN, Arenberg IK, Carver WF, Spector GJ, Stroud MH. Pre and post glycerol special audiometric test battery results in endolymphatic hydrops. Laryngoscope 1976; 86: 409-500.

33. Alford BR, chairman. Meniere's disease. Criteria for diagnosis and evaluation of therapy for reporting. Trans Am Acad Ophthalmol Otolaryngol 1972; 76:1462-4.

34. Arenberg IK, Brandenberg JH, Sauer RC, Kaemmerle AW. Reporting results in Meniere's disease according to the 1972 AAOO criteria: suggestion for standardization. Otolaryngol Clin North Am 1980; 13:681-92.

35. Marlowe FI. Drug treatment of Meniere's disease. Otolaryngol Clin North Am 1973; 6:119-30.

36. Weintraub J, Arenberg IK, Spector GJ, Stroud MH. The efficacy of "conservative" medical regimens on the rate of hearing losses in Meniere's syndrome: a retrospective computerized statistical analysis. Laryngoscope 1976; 86:1391-6.

37. Guilford FR. Treatment of Meniere's disease. In: Fields WS, Alford BR, eds. Neurological aspects of auditory and vestibular disorders. Springfield: Charles C Thomas, 1964:341.

38. Furstenberg AC, Lashmet FH, Lathrop F. Meniere's symptom complex: medical treatment. Ann Otol Rhinol Laryngol 1934; 43:1035-46.

39. Krejci F. Significance of ultrasonics in otolaryngology. Wien Klin Wochenschr 1962; 64:714.

40. James JA. Ultrasonic therapy for hydrops. Laryngoscope 1965; 75:1552-7.

41. Pennington CL, Stevens EL. Ultrasonic ablation of the labyrinth in the treatment of endolymphatic hypertension (Meniere's disease). South Med J 1969; 60:34-43.

42. House WF. Cryosurgery of the promontory. Otolaryngol Clin North Am 1968; 1:669-81.

43. Wolfson RJ, Cutt RA. Long-term results with cryosurgery for Meniere's disease. Arch Otolaryngol 1971; 93:483-6.

44. Glasscock ME, Miller GW, Drake FD, Kanok MM. Surgical management of Meniere disease with the endolymphatic-subarachnoic shunt: a five year study. Laryngoscope 1977; 87: 1668-75.

45. Gardner G. Endolymphatic sac shunt operation in Meniere's disease. Trans Am Acad Laryngol Otol 1975; 80: 306-13

46. Silverstein H. The effect of the endolymphatic subarachnoid shunt operation on vestibular function. Laryngoscope 1978; 88:1603-11.

47. Maddox ME. Endolymphatic sac surgery. Laryngoscope 1977; 87:1676-9.

48. Arenberg IK, Stahle J. Endolymphatic sac surgery for Meniere's disease: a comparison of the unidirectional inner ear valve and Silastic sheeting in patients with a minimum of one year follow up Am J Otol 1981; 2:329-34.

49. Arenberg IK, Stahle J. Unidirectional inner ear valve implants: a nondestructive alternative to labyrinthectomy in Meniere's disease. Am J Otol 1981; 3:9-10.

50. Brackmann DE, Anderson RC. Meniere's disease: treatment with the endolymphatic subarachnoid shunt. A review of 125 cases. Otolaryngol Head Neck Surg 1980; 88:174-82.

51. Krupin T, Kaufman P, Mandell A, et al. Filtering valve implant surgery for eyes with neovascular glaucoma. Am J Ophthalmol 1980; 89:338-43.

52. Clemis J, Valvassori GE. Recent radiographic and clinical observations of the vestibular aqueduct: a preliminary report. Otolaryngol Clin North Am 1968; 8:339-46.

53. Schuknecht HF. Pathology of Meniere's disease as it relates to sac and tack procedures. Ann Otol Rhinol Laryngol 1977; 86: 677-82

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AUDITORY BRAINSTEM RESPONSE WITH HIGH STIMULUS RATES IN NORMAL AND PATIENT POPULATIONS

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Normative data were collected on 48 subjects to determine the effects of increasing stimulus rates on the auditory brainstem response. These subjects were then compared to 221 patients referred for otoneurologic evaluation. The 90 patients with impaired auditory sensitivity demonstrated significantly less wave V latency shift than either the 131 patients with normal auditory sensitivity or the normal subjects. The incidence of abnormal wave V latency shift was 12% in the patients with normal auditory sensitivity and 8% in the patients with impaired auditory sensitivity. The high stimulus rate was often the only ABR parameter indicative of brainstem involvement in patients with documented CNS pathology. The authors conclude that a high stimulus rate contributes to the diagnosis of brainstem pathology often enough to warrant its routine use.

The auditory brainstem response (ABR) can provide objective and quantifiable information in the otoneurologic evaluation of the patient with suspected cochlear, retrocochlear, or central nervous system (CNS) pathology.[1-6] Utilizing AER to its maximum potential is primarily an exercise in identifying response patterns and knowing which values fall within the range of normal variation and which values have diagnostic significance for peripheral or brainstem dysfunction.[7,8]

The waves I-V interpeak latency (IPL) and the waves V/I amplitude ratio (AR) are common ABR parameters for determining central dysfunction. Of the two, the I-V IPL is more frequently utilized due to the multiple factors which affect the V/I AR.[3]

The diagnostic value of a third ABR parameter, use of a high stimulus rate, is quite controversial. Several authors have shown that increasing the stimulus rate and determining peak latency shifts is of value in identifying the presence of a demyelinating disease, anoxic-ischemic encephalopathy, tumor, or other brainstem abnormalities.[9-11] Despland and Galambos[10] have stated that the underlying rationale for rate studies is that in the presence of intracranial pathology, auditory pathways are more likely incapable of conducting neural impulses at high rather than low stimulus rates.

Chiappa et al[12] stated, however, that an increase in stimulus rate provides no greater diagnostic information than already present at a low stimulus rate. In addition, Rowe[4] has reported that although investigators have found that more subtle abnormalities may be detected, which are missed at low stimulus rates, this appears to be a rare occurrence. The basis of this controversy may be related to both the decrease in waveform resolution associated with high stimulus rates and the paucity of information on a large patient population regarding the incidence of stimulus rate abnormality.

The purpose of this investigation was to determine whether increasing the stimulus rate provides diagnostic information often enough to warrant its routine inclusion in the ABR test battery. To accomplish this goal, the effects of high stimulus rates on a normal adult population were compared with results obtained on a large clinic population referred for otoneurologic evaluation.

METHODS

Subjects. Normative data were collected on 48 adult subjects from 20 to 35 years of age with audiometric thresholds no greater than 15 dB HL (re ANSI-1969) at octave and interoctave frequencies from 250 through 8,000 Hz and no history of neurologic involvement. The normative data were then compared to the ABR results on 221 clinic patients, which included 131 with normal peripheral hearing sensitivity and 90 with impaired hearing sensitivity. All patients were greater than 18 months of age which allowed comparison to adult normative rate data.[11]

Instrumentation. Standard electroencephalograph (EEG) goldcup disc electrodes were attached to the vertex and each mastoid. The vertex electrode was active with the mastoid electrode ipsilateral to the stimulus as reference, and the contralateral mastoid electrode as ground. Interelectrode impedance was less than 6 KΩ. Electrodes from the patient were connected to a preamplifier (Grass model P-511) where the EEG was bandpassed from 300 to 3,000 Hz and amplified by 100,000 before oscilloscopic display and analysis by a computer averager (Nicolet model 1072). The window was 20.48 ms, ie, 512 memory addresses at a 40-ms dwell time.

The stimulus was a 100 μs rarefaction electric pulse produced by a pulse generator (Grass model S-48) and delivered monaurally to an electromagnetically shielded earphone with cushion (TDH-49, MX-41AR). The primary energy peak in the acoustic spectrum of the transduced electric pulse was in the 3,000 Hz region. Click intensities were referred to the average psychophysical click threshold of audiometrically normal adult listeners. At an intensity 60 dB above this reference, or 60 dB nHL, with an interstimulus interval of 50 ms, a reading of 67 dB SPL was obtained.

Both the EEG and output from the pulse generator were monitored on an oscilloscope during testing. Each average response

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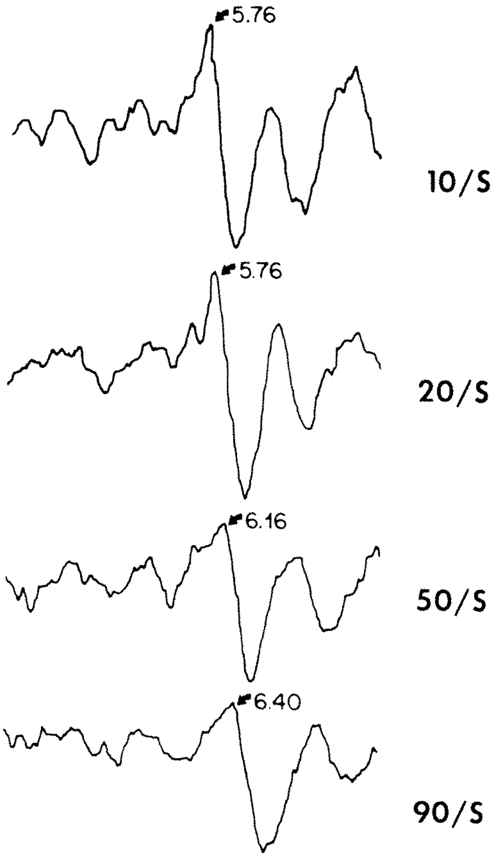

Fig 1. Auditory brainstem response with wave V latency (ms) shown at four stimulus rates for a typical subject.

was based on 2,048 click presentations replicated once and summed for a total of 4,096 at each intensity. Patients were tested while recumbent during natural or sedated sleep in a double-walled IAC (International Acoustic Corp.) booth.

RESULTS

Normative Findings. The effects of increasing stimulus rate from 10 to 20, 50, and 90 clicks per second with intensity held constant at 60 dB nHL are shown for one subject in Figure 1. Note the increase in latency of wave V and overall decrease in ABR amplitude as stimulus rate increases from 10 to 90/s. The mean latency of wave V at each of the four rates is shown in Table 1. All wave V latencies were significantly different from each other ($p < .05$) except for the 10 to 20/s comparison ($p > .10$). Analysis was accomplished using a repeated measures analysis of variance (ANOVA) and the Newman-Keuls multiple comparisons test.[13] To minimize test time and maximize the effect of rate, the latency shift between 20 and 90/s ($p < .001$) has been used in the routine clinical ABR evaluation.

To determine the effect of intensity on the wave V latency shift from 20 to 90/s, data were collected on two separate subject groups. The first group was tested at 30, 60, and 70 dB nHL, and the second group at 40, 60, and 70 dB nHL. The means and standard deviations are presented in Table 2. The greatest shift of latency between means was 0.11 ms with no detectable trend over the four intensities. Group data were analyzed using a repeated measures ANOVA.[13] No significant intensity effect was found for either group ($p > .05$). These results are in agreement with the findings of Don et al.[14]

TABLE 1. MEANS AND STANDARD DEVIATIONS OF WAVE V LATENCY (MS) AT FOUR STIMULUS RATES WITH INTENSITY CONSTANT AT 60 dB nHL

	Clicks/Second			
	10	*20*	*50*	*90*
N	12	12	12	12
Mean	6.13	6.17	6.52	6.81
SD	0.30	0.31	0.39	0.35

nHL = Normal hearing levels; N = No. of subjects.

The difference between the wave V latency means for rates of 20 and 90/s at 60 dB nHL for all 48 normal subjects was 0.61 ms with a standard deviation of 0.14 ms and a range in scores of 0.24 to 0.96 ms. The criterion for an abnormally large shift of wave V latency was defined as greater than three standard deviations above the mean (>1.04 ms).

Patient Findings. Figure 2 shows the distribution of the wave V latency shift for a stimulus rate change from 20 to 90/s for the normal subjects, the hearing-impaired patients, and the normal hearing patients. Note that the distribution of the hearing-impaired patients was shifted toward an overall shorter latency shift than either the normal-hearing patients or subjects. The three distributions were analyzed using an ANOVA by ranks and the Dunn multiple comparisons test.[15] These nonparametric tests were necessary due to the expected significant differences ($p < .05$) between distribution variances as demonstrated by the F test.[13] Analysis revealed the two patient distributions as significantly different ($p < .001$). In addition, the subject and hearing-impaired patient distributions were also significantly different ($p < .01$), but not the subject and normal-hearing patient distributions ($p > .5$).

Sixteen of the 131 normal-hearing patients, or 12%, had wave V latency shifts that exceeded the 1.04 ms criterion defined previously (>3 SD). Seven of the 90 hearing-impaired patients, or 8%, also demonstrated prolonged wave V latency shifts despite the reduced stimulus rate effect described above. An example of latency abnormality is shown in Figure 3A. The wave V latency shift was from 6.4 to 8 ms, or 1.6 ms. The earlier wave components frequently become less distinct at a high rate of

TABLE 2. MEANS AND STANDARD DEVIATIONS OF THE WAVE V LATENCY SHIFT (MS) FROM 20 TO 90/S AT FOUR INTENSITIES IN TWO SUBJECT GROUPS

	dB nHL					
	30	*40*	*60*		*70*	
N	11	13*	11	13*	11	13*
Mean	0.66	0.55*	0.65	0.65*	0.55	0.55*
SD	0.20	0.19*	0.11	0.16*	0.10	0.14*

*Data from the subject group tested at 40, 60 and 70 dB nHL. The other group was tested at 30, 60 and 70 dB nHL.

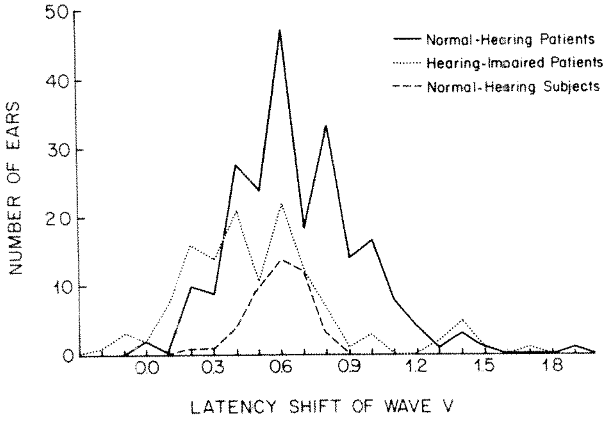

Fig. 2. Distributions for wave V latency shift from 20 to 90/s for each group. Each point represents an interval of data, eg, data point 1.2 = 1.15-1.24 ms.

stimulation. Eleven additional hearing-impaired patients had either severely reduced amplitudes (8 patients) or completely absent ABR (3 patients). In Figure 3B, this second abnormal pattern is shown. Note the dramatic reduction in the amplitude of the response making even the selection of wave V difficult. This less frequent pattern was seen only in the hearing-impaired patients.

Of the 16 normal-hearing patients with abnormal wave V latency shifts, 10 were children aged 2 to 8 years. Nine of these 10 children had significant neurologic findings consisting of spasticity, seizures, and psychomotor retardation. In four cases, the pathology was secondary to documented hypoxic-ischemic episodes in the prenatal or neonatal period. In spite of the high incidence of neuropathology, a high stimulus rate was the only ABR test parameter indicative of brainstem involvement. The following case histories are illustrative.

CASE REPORTS

Case 1. A female twin, aged 3 years and 11 months, was referred by an otolaryngologist to rule out hearing impairment. She presented with seizures and hypertonicity in the lower extremities, and was diagnosed as microcephalic and spastic quadriplegic, secondary to hypoxic ischemic encephalopathy. ABR results indicated no evidence of impaired auditory sensitivity. However, intrinsic brainstem abnormality was indicated by a prolonged wave V latency shift at the 90/s rate when the right ear was stimulated.

The patient's identical twin sister was also evaluated by ABR and demonstrated no auditory abnormalities. This identical twin has thus far exhibited normal psychomotor development.

Medical histories of the six adult patients, aged 37 to 53 years, with normal hearing but abnormal wave V latency shift, included head trauma, spasmodic dysphonia, and suspected cases of multiple sclerosis, peripheral neuropathy, or myasthenia gravis. In these patients, the abnormal ABR finding, apparent only at the high stimulus rate, was often considered a confirming indication of organic CNS pathology.

Case 2. A 53-year-old female was diagnosed as having spasmodic dysphonia and referred by a neurologist for suspected CNS involvement. Her speech disorder had existed for four years and had increased in severity just prior to evaluation. Neurologic symptoms included ptosis of the left eye, dysphagia, migraine headaches with impaired vision, and numerous scotoma. Subsequent testing ruled out myasthenia gravis. ABR results pointed to intrinsic brainstem abnormality due to prolonged latency shifts at the 90/s rate when either the right or left ear was stimulated.

The abnormal ABR finding in Case 2 led to additional research on spasmodic dysphonia by the authors. An abnormal ABR was seen only with the use of the high stimulus rate in 4 of 6 spasmodic dysphonia patients tested.[6]

Of the 7 hearing-impaired patients with identifiable and prolonged wave V latency shifts at the 90/s rate, 4 were aged 2 to 4 years. All four children had substantial psychomotor retardation and one was diagnosed as spastic quadriplegic. The three adults, aged 34 to 44 years, had etiologies of demyelinating disease, spasmodic dysphonia, and head trauma. Both a pediatric and an adult case history are presented.

Case 3. A 3-year-old female was referred by a neurologist who subsequently diagnosed her as having familial dysautonomia, a disease characterized by defective lacrimation, motor incoordination, hyporeflexia, and mild psychomotor retardation. Nystagmus was present at midposition, and most prominent on left lateral gaze with horizontal and rotary components. An older sibling with dysautonomia had evidence of demyelination not yet found in this patient. ABR and impedance results indicated a mild bilateral conductive hearing loss. Intrinsic brainstem abnormalities were suggested by a prolonged IPL and an abnormal AR stimulus in the right and left ears respectively. In addition, a prolonged wave V latency shift at the 90/s rate was found when the left ear was stimulated.

Case 4. A 36-year-old male involved in a high-impact motor vehicle accident was referred by an otologist to determine the extent of otoneurologic pathology secondary to a right frontotemporoparietal compound, comminuted skull fracture with small epidural hematoma. Findings at surgery included a small dural tear overlying the sylvian fissure just above the right temporal lobe and an orbital roof fracture with marked intraorbital tissue edema. The patient subsequently underwent cranioplasty. Audiometric tests completed six months postoperatively revealed a bilateral precipitous high-frequency loss above 4,000 Hz, significant tone decay at 4,000 Hz for the left ear, and abnormally low central scores on the Staggered Spondaic Word Test (SSW) and dichotic digits for the left ear. ABR results indicated intrinsic brainstem abnormality due to a prolonged latency shift at the 90/s rate when the left ear was stimulated.

DISCUSSION

A primary objective in this study was to evaluate the efficacy of a high stimulus rate in identification of intracranial pathology in a large clinic population. Twenty-two of 23 patients with prolonged wave V latency shifts were identified only at the high stimulus rate as having CNS involvement. The other patient (case 3) had both interpeak latency (IPL) and amplitude ratio (AR) abnormalities. This study demonstrated the utility of the 90/s rate in clinical ABR evaluation.

The rationale for using the relative wave V latency shift to develop normative data was based on previous findings of both a greater stability in amplitude and a greater effect on the latency of wave V when compared to earlier wave components.[2,14,16-18] The stability of the wave V amplitude made determination of latency shift possible in all but 11 of our 221 patients. The large effect of the 90/s rate on wave V latency allows differentiation of rate effect from smaller nonpathological factors

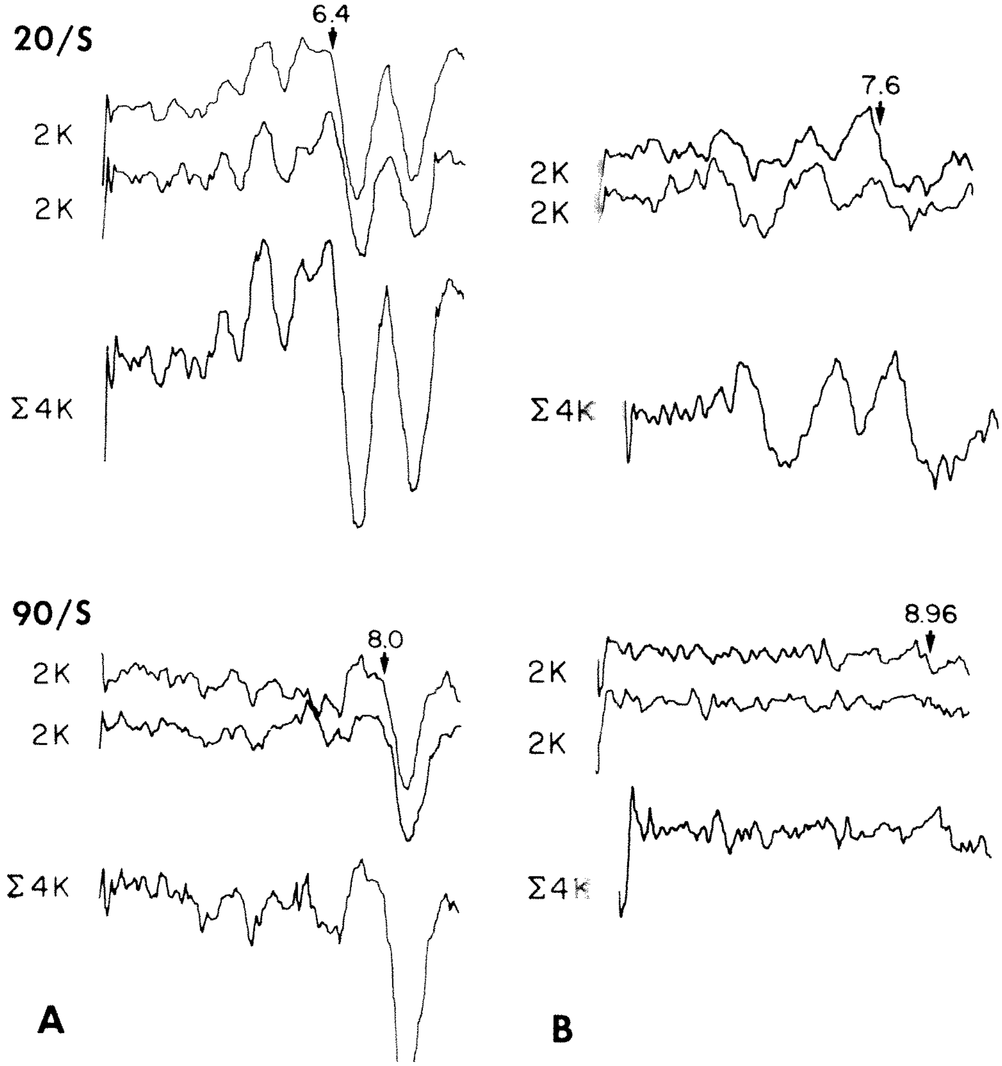

Fig 3. Patterns of abnormal latency shift from the 20 to 90/s rate. Stimulus intensity was 60 dB nHL. A) Most frequent; B) less frequent.

such as intersubject and intrasubject variability. Furthermore, the relative latency shift of wave V was not significantly dependent upon intensity through 70 dB nHL, thus facilitating its clinical application.

The earlier waves I-IV were often substantially reduced in amplitude which made definitive IPL measures difficult. However, this was not considered a significant drawback to the diagnostic value of high stimulus rate. Achor and Starr,[19] in a study of the effects of discrete lesions in cats, demonstrated that the ABR components generated rostral to the eighth cranial nerve have substantial contributions for more than one auditory brainstem structure. For this reason, an ABR abnormality should be used to document the presence of neuropathology, rather than to identify a specific correlation between a given brainstem site and a particular wave.[4] Thus, at present, it would appear that maximizing the effect of stimulus rate on the ABR is more important diagnostically than identifying each of the components in an attempt to localize a lesion along the brainstem.

In 1975 Thornton and Coleman[18] presented data supporting a hypothetical model in which adaptation due to high stimulus rates occurred from auditory nerve through rostral brainstem in normal subjects. Neurophysiologic mechanisms considered responsible for observed latency shifts with increased rate when both peripheral and central auditory systems are intact include a change in cochlear receptor function,[14] the refractory period of neural elements, and a decrease in synaptic efficacy.[20] In pathological conditions, these mechanisms are probably altered resulting in the observed prolonged latency shifts and/or absence of the ABR when stimulus rate is increased.[17,21]

Pratt et al[21] stated that a high stimulus rate appeared sensitive to a subset of their patients and suggested that rate may augment ABR abnormalities for patients with nuclear rather than fiber lesions. However, in the case of a fiber lesion patient who did not show a rate abnormality, two variables may have affected the interpretation. First, only a 50/s rate was used, whereas a 90/s rate may have had a greater effect on the ABR. Second, the patient had a 60 dB hearing loss. In the current investigation, hearing loss shortened the latency shift.

With the exception of Coats and Martin,[22] the literature has not dealt with the implications sensory hearing impairment might have on the interpretation of ABR in CNS pathology. These authors demonstrated shorter I-V IPL in their hearing-impaired versus normal-hearing groups, and cautioned that separate normative data would improve the sensitivity of the IPL parameter in the diagnosis of CNS pathology.

The present study provides further support for caution when the patient with suspected CNS pathology also has impaired hearing. Using norms based upon normal-hearing subjects for patients with hearing impairment would allow a much higher false-negative error. Thus, additional investigation into the nature of the shortened latency shift in patients with sensory hearing loss is now in progress to establish a more efficient criterion of abnormality.

In summary, Hecox et al[11] stated that a stimulus which is optimal for eliciting the most easily identifiable ABR waveform may not be optimal for demonstrating pathology. In fact, this study has demonstrated that patients with CNS pathology, such as spastic quadriplegia or severe head trauma, may manifest an abnormality only at a high stimulus rate. The conservative approach in defining the criterion of abnormality in this study allowed only a 1% false-positive error, which conversely increased the risk of false-negative error. Despite this, the incidence of 12% in the normal-hearing and 8% in the hearing-impaired patients was significant in the detection of brainstem pathology. For this reason, it is recommended that routine testing of all patients include a low and high stimulus rate to aid in documenting intracranial pathology.

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REFERENCES

1. Galambos R, Hecox KE. Clinical applications of the auditory brain stem response. Otolaryngol Clin North Am 1978; 11:709-22.

2. Starr A, Sohmer H, Celesia GG. Some applications of evoked potentials to patients with neurological and sensory impairment. In: Callaway E, Tueting P, Koslow SH, eds. Event-related brain potentials in man. New York: Academic Press, 1978: 155-96.

3. Stockard JJ, Stockard JE, Sharbrough FW. Brainstem auditory evoked potentials in neurology: methodology, interpretation, clinical application. In: Aminoff MJ, ed. Electrophysiologic approaches to neurologic diagnosis. New York: Churchill Livingstone, 1979: 541-67.

4. Rowe MJ. The brainstem auditory evoked response in neurological disease: a review. Ear Hear 1981; 2:41-51.

5. Hecox KE. Galambos R. Brain stem auditory evoked responses in human infants and adults. Arch Otolaryngol 1974; 99:30-3

6. Finitzo-Hieber T, Freeman FJ, Gerling IJ, Dobson L, Schaefer SD. Auditory brainstem response abnormalities in patients with adductor spasmodic dysphonia. Am J Otolaryngol 1982; 3:26-30.

7. Stockard JJ, Stockard JE, Sharbrough FW. Nonpathologic factors influencing brainstem auditory evoked potentials. Am J EEG Technol 1978; 18:177-209.

8. Thornton ARD. The development of statistical diagnostic criteria in surface-recorded electrocochleography. In: Stephens SDG, ed. Disorders of auditory function II. London: Academic Press, 1976: 127-38.

9. Stockard JJ, Stockard JE, Sharbrough FW. Detection and localization of occult lesions with brainstem auditory responses. Mayo Clin Proc 1977; 52: 761-9.

10. Despland PA, Galambos R. The auditory brainstem response (ABR) is a useful diagnostic tool in the intensive care nursery. Pediatr Res 1980; 14:154-8.

11. Hecox K. Cone B, Blaw ME. Brainstem auditory evoked response in the diagnosis of pediatric neurologic diseases. Neurology 1981; 31:832-40.

12. Chiappa KH, Gladstone KJ, Young RR. Brain stem auditory evoked responses: studies of waveform variations in 50 normal human subjects. Arch Neurol 1979; 36:81-7.

13. Zar JH. Biostatistical analysis. Englewood Cliffs: Prentice-Hall, 1974.

14. Don M, Allen AR, Starr A. Effect of click rate on the latency of auditory brain stem responses in humans. Ann Otol Rhinol Laryngol 1977; 86:186-95.

15. Hollander M, Wolfe D. Nonparametric statistical methods. New York: John Wiley and Sons, 1973.

16. Hyde ML, Stephens SDG, Thornton ARD. Stimulus repetition rate and the early brainstem responses. Br J Audiol 1976; 10:41-6.

17. Yagi T, Kaga K. The effect of the click repetition rate on the latency of the auditory evoked brain stem response and its clinical use for a neurological diagnosis. Arch Otorhinolaryngol 1979; 222:91-6.

18. Thornton ARD, Coleman MJ. The adaptation of cochlear and brainstem auditory evoked potentials in humans. EEG Clin Neurophysiol 1975; 39:399-406.

19. Achor JL, Starr A. Auditory brain stem responses in the cat. II. Effects of lesions. EEG Clin Neurophysiol 1980; 48: 174-90.

20. Pratt H, Sohmer H. Intensity and rate functions of cochlear and brain stem evoked responses to click stimuli in humans. Arch Otorhinolaryngol 1976; 212:85-92.

21. Pratt H, Ben-David Y, Peled R, Podoshin L, Scharf B. Auditory brain stem evoked potentials: clinical promise of increasing stimulus rate. EEG Clin Neurophysiol 1981; 51:80-90.

22. Coats AC, Martin JL. Human auditory nerve action potentials and brain stem evoked responses: effects of audiogram shape and lesion location. Arch Otolaryngol 1977; 103:605-22.

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EPIDERMOID CYSTS OF THE VOCAL CORDS

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Fifty-three cases of intracordal epidermoid cysts diagnosed, treated and followed from 1972 to 1981 are presented. In the clinical evaluation, special attention must be paid to the type of dysphonia and morphology of the vocal cords at indirect laryngoscopy. The epidermoid cyst is not easily visualized and the examiner must take into account signs like "monochorditis," slight bulging, unilateral nodule and diminished or abolished vibrations of one of the cords at stroboscopy. Microsurgical excision followed by voice therapy is the recommended treatment. The pathogenesis of these cysts is still speculative. Two theories are discussed: the traumatic theory and the dysembryoplastic theory.

Epidermoid cysts may be encountered within the vocal cords. The diagnosis is usually difficult because of the relative scarcity of clinical signs. These intracordal cysts can be excised using microsurgical techniques. Generally the intracordal cysts described in the literature consist of retention or mucus cysts, most probably caused by obstruction of a glandular duct. These retention cysts are considered the most frequent type of vocal cord cysts. Epidermoid cysts have been infrequently reported in the literature.[1] Ash and Raum[2] present a concise histological description in which they attribute cause to possible trauma. Vocal cord epidermoid cysts bear a strong resemblance to epidermal cysts of the skin.[3,4] An analogy can also be made with the histologic structure of cholesteatoma.[5]

In the present series, 53 cases of epidermoid cysts of the vocal cords are reported and their clinical, surgical and histopathological features are considered.

METHODS

Of the 53 patients with intracordal epidermoid cysts operated upon from 1972 to 1981, 45 were women and 8 were men. Their ages varied from 8 to 52 years; most patients ranged between the ages of 21 and 40. All 53 patients underwent a thorough clinical phoniatric evaluation consisting of a careful history, a subjective acoustical voice evaluation, a complete otolaryngological examination including indirect laryngoscopy, and a stroboscopic evaluation. All underwent surgical removal through suspension-direct laryngoscopy (under general anesthesia). A Zeiss microscope with a 12.5 magnification eyepiece and a 350-mm objective lens was used with the magnification dial set at 25.

After an evaluation of the lesion through the microscope and gentle palpation, an incision was made on the surface of the cord to open the mucosa just medial to the vocal ligament (Fig 1). The cyst was dissected and removed. The cavity created by the removal of the cyst was then carefully inspected in order to insure that no remnant or other cyst remained. The margins of incision were allowed to join together to close the wound, and an intracordal injection of hydrocortisone acetate completed the procedure. All specimens were examined by a pathologist.

RESULTS

Clinical Findings. In all patients, the reason for consultation was dysphonia. Since 29 were professional voice users, or involved in amateur singing or acting, even a small degree of phonatory difficulty was sufficient to bring them to the phoniatrician.

The voice was generally altered and sometimes the dysphonia was quite marked; tonality was lowered in both women and men The variability of voice intensity among the patients did not follow a specific pattern but vocal quality was frequently described by the consulting phoniatrician as "forced," husky, hoarse, tiring easily, or characterized by breaks in the voice and double tones.

A special effort was made in the history-taking to find a causative factor. The onset of dysphonia could be related to some degree of irritation of the vocal cords from vocal abuse (13 cases), infection (laryngitis, frequent sore throat, 9 cases), exposure to cold air (4 cases), coughing (2 cases), exposure to chemical irritants (1 case) and attempted strangulation (1 case). It was also found to be related to irritation experienced after throat operations (tonsillectomy, polyp removal on the vocal cord, 2 cases). Sometimes two of these factors could be related, eg, throat infection and vocal abuse (2 cases). Indirect laryngoscopy was often disappointing because cystic formation was rarely evident as such. In the majority of cases, a unilateral diffuse swelling of the cord ("monochorditis") was one of the most significant clues (33 cases). This sign may or may not be associated with a more localized submucosal bulging. When the latter is present, the diagnosis is more easily made. It was not uncommon to first visualize the contact lesion on the opposite cord (16 cases) which may manifest itself by a thickening of the free border of the cord, a nodule or a pseudocyst. However, the diagnosis is almost certain when, with the stroboscope, the vibrations

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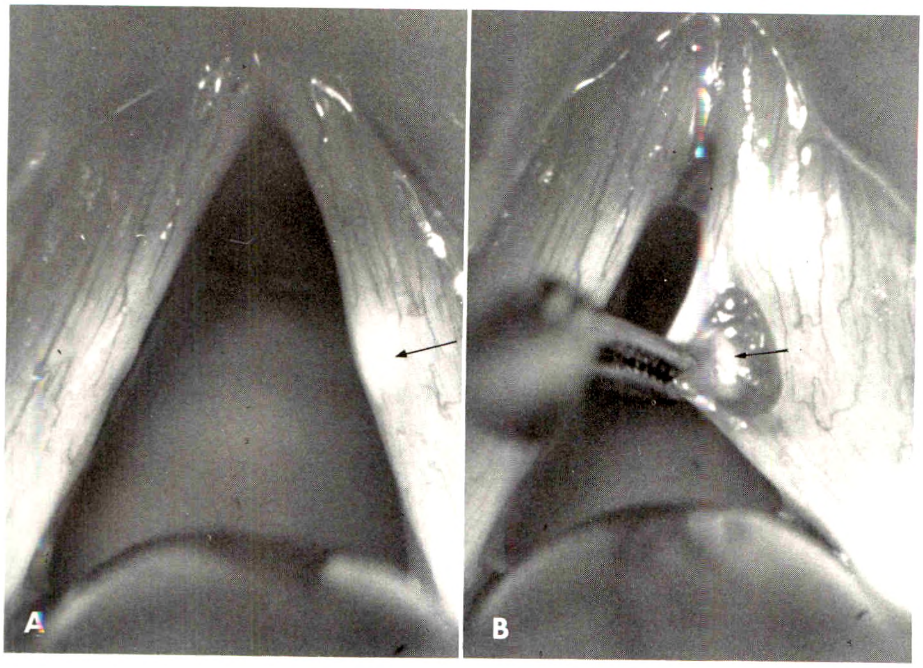

Fig. 1. Epidermoid cyst of right vocal cord. A) Before incision (arrow). B) After incision, cyst exposed medial to vocal ligament (arrow).

of the cystic cord are absent or at least markedly reduced.

Surgical Findings. In six cases, cysts were found on both cords and were removed either simultaneously (2 cases) or in two steps (4 cases). Also a recurrence was noted in the same cord of one patient. Two cysts were removed simultaneously from the same cord in one patient and three cysts from the same cord in another patient.

In the 53 patients, a total of 28 epidermoid cysts were found in the left cord and 18 in the right cord; six were bilateral; and the site was not recorded for one patient. Generally the cyst was located in the middle third of the cord just beneath the free border of the vocal fold; it appeared less frequently in the anterior or posterior part of the cord. The cyst was imbedded between the vocal ligament and the cordal mucosa (Fig 1B) and was never found within the muscular mass itself.

The intracordal epidermoid cyst was often associated with other lesions of the vocal cord(s). Forty-two patients had one or more associated lesions of the vocal cords, often suspected or diagnosed through indirect laryngoscopy but observed or confirmed at the time of surgery. These included unilateral or bilateral vocal cord sulcus (21 cases), nodules (at different stages of formation, 15 cases), "mucous bridge," (a longitudinal narrow band of cordal mucosa lying just over the opening of a sulcus or furrow, with anterior and posterior insertions on the free edge of the cord, 6 cases), chronic laryngitis and/or Reinke's edema (5 cases), polyp (2 cases), vasodilatation on the surface of the cord (1 case), and angiomatous nodule (1 case). Nodules, when present, were always located on the opposite cord.

Pathological Findings. Two kinds of epidermoid cysts were encountered, the true epidermoid cyst lined by normal malpighian epithelium and filled with keratin material (Fig 2), and the epidermoid inclusion cyst consisting of a solid malpighian epidermoid formation without keratin, which may represent an earlier stage in the formation of the cyst but is not really a cyst in itself.

DISCUSSION

The discussion of the pathogenesis of these cysts may prove to be purely speculative since, up to now, there is no scientific certainty as to the mechanism of formation of the epidermoid cysts of the vocal cord. An interesting hypothesis is the "traumatic theory,"[2] in which it is presumed that the development of the epidermoid cyst inside the vocal cord follows the same pattern as in the skin. Microtraumatisms from vocal abuse, inflammation or direct trauma could produce a small fissure into the cordal epithelium and would favor inclusion of a minute fragment of external cordal epithelium that would grow after healing of the original microwound and would follow a course somewhat similar to epidermal inclusion cysts of the skin or even cholesteatoma.

In this series, the onset of the dysphonia coincided with one of the previously mentioned factors in 27 instances. Also, among the 53 patients, 24 had the habit of screaming frequently or speaking with a loud voice.

Another interesting hypothesis may be considered,[6,7] the dysembryoplastic theory, which is based on the fact that epidermoid intracordal cysts are frequently associated with vocal cord sulcus and/or "mucous bridges."

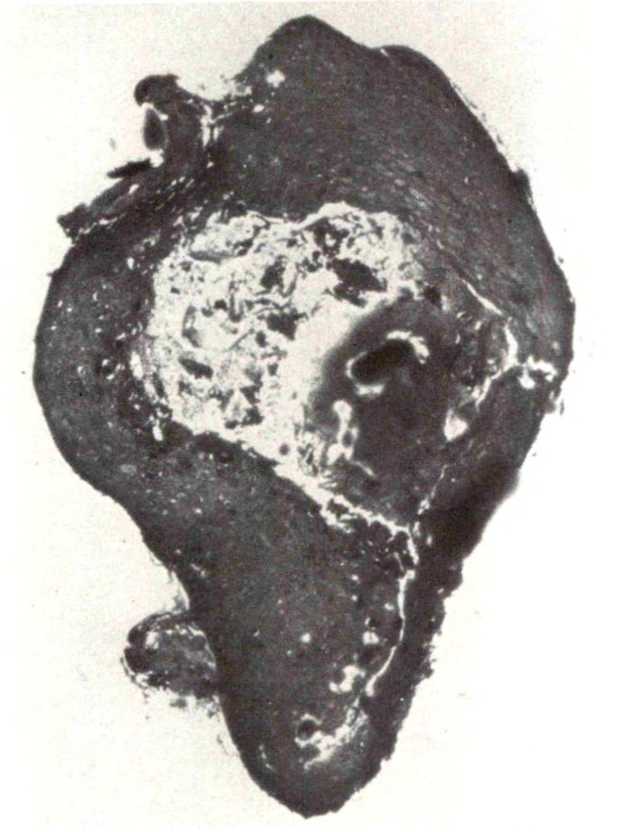

Fig. 2. Histological specimen of epidermoid cyst. Thick squamous epithelium with numerous keratinized cells. (x25)

Vocal cord sulcus was recognized as early as 1901.[8] Its embryogenic etiology was considered by Luchsinger and Arnold whose definition may be cited: "The congenital vocal cord sulcus is a fine longitudinal furrow on the medial edge of the vocal cord. It may extend along the entire length of the cord or it may be limited to a segment of variable length. Its depth is also variable and may range from a faint line to a deep partition of the cord."[9] According to Cornut and Bouchayer,[6,7,10] the vocal cord sulcus could be a stage in the development of epidermoid cysts of the vocal cord. During the surgical procedure for sulcus removal, it is not rare to find a cyst or keratin flakes imbedded in its deepest part. The long-standing dysphonia in many sulcus patients is another clue in favor of the embryogenic theory. As mentioned above, 21 of the 53 patients exhibited also a unilateral or bilateral vocal cord sulcus, and a "mucous bridge" was found just over the opening of the sulcus in six cases. Among the 21 cyst patients whose lesions were associated with sulcus, the dysphonia was reported to have been present "always" or for "many years" in 12 cases. This points more in favor of the dysembryogenic hypothesis than of the traumatic theory. For the other patients whose dysphonia appeared after inflammation or trauma, it may be assumed that inflammation provoked some degree of swelling in the already existing epidermoid cyst and stimulated the production of keratin materials. The congenital cyst would then grow to some extent and become symptomatic.

Intracordal epidermoid cysts have certainly existed for a long time but were infrequently reported most likely because diagnosis is difficult. The first clue for the experienced phoniatrician is the acoustic quality of the voice. However, the difficulty is that very often no cyst is visualized at indirect laryngoscopy; one sees normal cords or a slight enlargement of one cord (Fig 1A), or some degree of inflammation on one side (monochorditis), or even the contact lesion on the opposite cord. In that case, the patient may be operated upon for a unilateral nodule. The correct diagnosis is often missed because the cyst itself is not visible. If there is a lack of vibrations at stroboscopic examination, the diagnosis may be strongly suspected. The clinical aspect of the cystic cord maybe easily explained. Even if the epidermoid intracordal cysts are relatively small (their size may vary from approximately 1 to 4 mm), the cordal epithelium over the growing cyst becomes tense and its free movement over the vibrating cord becomes impaired. Because of abnormal vibrations, the patient experiences some difficulty in producing normal sounds since cords are strained during speech. Since the lesion remains and does not subside by itself, some tension is added in the phonatory mechanism every time a sound is made. The cystic cord often becomes inflamed because of the persisting process of tension. In addition, the opposite cord may develop a thickening which may evolve into a nodular formation.

CONCLUSION

Epidermoid intracordal cysts are not a rare entity although they are not frequently reported in the literature. With the sophistication of microlaryngeal instrumentation, they have become more easily accessible. The diagnosis remains difficult; the history-taking must be carefully obtained and special attention must be given to long-standing stable dysphonia. Also the character of the dysphonia itself is an important diagnostic element particularly to a trained ear. A lowered tonality with a husky, hoarse, desonorized quality, and a voice getting easily tired and produced with effort should alert the phoniatrician.

At indirect laryngoscopy the fact that nothing much can be seen to explain the audible dysphonia is a clue in itself. A unilateral cordal enlargement or inflammation (monochorditis) should be suspected. Furthermore, if the glottal slit is oval, the suspicion of a cyst is enhanced. Stroboscopy confirms the suspicion; a decrease or absence of mucosal vibrations on a phonating cord is an abnormal clinical finding, indicating disease within the cord. Unless this is related to a scar from previous surgery or trauma, the nonvibrating cord should be surgically explored.

Differential diagnosis remains to be made with a nonspecific monochorditis and a vocal cord sulcus; these entities may all be easily confused. A nonspecific monochorditis, without an intracordal mass, should not show a lack of vibration at stroboscopy. Also it would be expected to subside with the proper medical treatment.

The symptoms and signs of vocal cord sulcus bear strong resemblance to those of intracordal cysts. Acoustically, male vocal tonality in sulcus is generally elevated while it is lowered in cysts; female vocal tonality is lowered with both sulcus and cysts. Sometimes a groove may be seen just under the free border of a cord, which is typical of the sulcus, but this sign is not always evident at indirect laryngoscopy. Cordal inflammation may also be seen and stroboscopic examination may show a diminished vibratory pattern. Even if an experienced phoniatrician usually can make the differential diagnosis, surgical exploration confirms the final diagnosis and is indicated in both instances. Once the presence of the cyst is clinically established, it is usually impossible to be sure of its histologic structure. It may be a retention cyst or an epidermoid cyst. The retention cyst tends to be larger than its epidermoid counterpart and thus is more evident at indirect laryngoscopy. The diagnosis is, then, more easily made, but the final histological diagnosis is made by the pathologist.

Surgical removal is the treatment of choice, combined with vocal reeducation support for vocal improvement. This aspect is especially important for professional voice users. If surgery is refused by the patient, vocal reeducation may bring some vocal improvement especially if it aims at diminishing the vocal effort, but the dysphonia will persist and the forcing habits may well recur.

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REFERENCES

1. Kleinsasser O. Microlaryngoscopy and endolaryngeal microsurgery. Hoffman PW, trans. Philadelphia: WB Saunders, 1968.

2. Ash JE, Raum M. An atlas of otolaryngologic pathology. 4th ed. Washington: American Registry of Pathology, 1956.

3. Anderson WAD, Scotti IM. Synopsis of pathology. St. Louis: CV Mosby, 1972.

4. Lever WF, Schaumburg-Lever G. Histopathology of the skin. Philadelphia: JB Lippincott, 1975.

5. Schechter G. A review of cholesteatoma pathology. Laryngoscope 1969; 79:1907-20.

6. Bouchayer M, Cornut G. Cystes et pseudolystes de la corde vocale (à propos de 32 cas). Compte-rendu des Séances du congrès francais d'O.R.L.: Arnette'Paris, 1974.

7. Cornut G, Bouchayer M. Indications phoniatriques et résultats fonctionnels de la microchirurgie laryngée. Bulletin d'audiophonologie 1977; 7:5-52.

8. Salvi G. Anomalia laryngis humani. Arch Psychiatr 1901; 22:369.

9. Luchsinger R, Arnold GE. Voice, speech, language, clinical communicology: its physiology and pathology. Belmont: Wadsworth Publishing, 1965:171-5.

10. Bouchayer M, Cornut G. Le sulcus glottidis — notions nouvelles apportées par la microchirurgie laryngée (ã propos de 31 cas). Les cahiers d'O.R.L. 1978; 13(8):769-77.

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PATHOLOGY OF JUGULAR FORAMEN NEUROFIBROMA

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Tumors of jugular foramen may closely resemble glomus jugulare tumors clinically and radiographically. A tissue diagnosis is necessary to make a differentiation of these tumors. This conclusion is supported by the findings in a temporal bone from a patient who was diagnosed clinically as having a glomus jugulare tumor 57 years before her death at the age of 84 years. Compression of the 7th and 8th cranial nerves in the internal auditory canal and the 10th and 11th cranial nerves at the jugular foramen represents the mechanism of neural signs produced by a neurofibroma arising in the jugulare foramen. This case further demonstrates that conservative treatment of benign extradural tumors may be compatible with a long and useful life.

INTRODUCTION

The most common benign tumor arising in the jugular foramen and middle ear is the glomus jugulare tumor.[1-4] Since the differential diagnoses vary from anatomical variants to malignant tumors, a number of clinical entities may simulate the glomus jugulare tumor.[5] Most of these conditions can be excluded from the differential diagnosis by careful clinical and radiographic examination. However, a small number of benign neoplasms arising in the jugular foramen are so similar in their clinical and radiographic appearance that an accurate diagnosis can only be made by tissue biopsy.[6] Since the treatment of these tumors varies greatly, precise diagnosis is essential.

The present case report illustrates this point by providing histological verification of a neurofibroma in the temporal bone specimen from a patient who demonstrated the clinical presentation of a glomus jugulare tumor[7] 57 years prior to death. This temporal bone not only underscores the clinical similarity of these two tumors, but also demonstrates the mechanism by which various neurovascular deficits are produced and the fate of a neurofibroma not surgically excised.

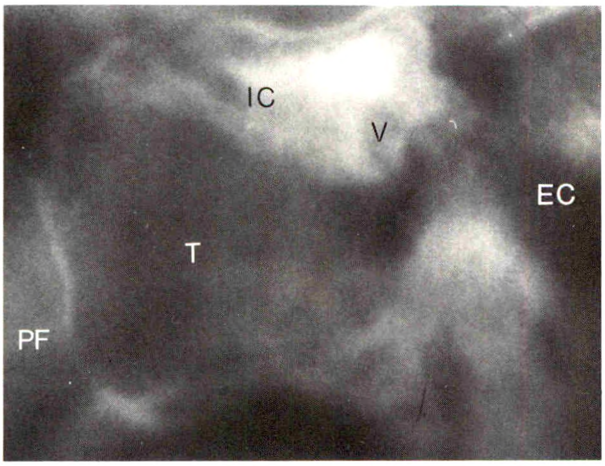

Fig. 1. Coronal tomogram demonstrating osteolytic lesion (T) arising in jugular foramen and compressing internal auditory canal (IC). V - Vestibule; EC - External auditory canal; PF - Posterior fossa.

CASE REPORT

The patient was a female who in 1921 at the age of 25 years first noted a change in her singing voice in that there was a loss of the ability to reach high frequencies. She had also complained of slight imbalance and a mild loss of hearing in the right ear. In 1923 because of a facial weakness which had occurred over a 6-week period, the patient was evaluated by Dr. H. Cushing who found a complete right facial paralysis, in addition to paralysis of the 9th, 10th and 11th cranial nerves. On the basis of a clinical suspicion of a cerebellopontine tumor, the patient received three radiation treatments (total approximately 500-1000 rad). Following this treatment, the facial paralysis improved but the remaining cranial nerve deficits were unchanged.

The patient was followed in subsequent years with supportive medical treatments consisting of decongestants and allergy treatments. Radiographic evaluation demonstrated an osteolytic lesion of the jugular foramen with narrowing of the internal auditory canal (Fig. 1). During that period of time, the patient noted a progressive right-sided hearing loss (Fig. 2) and intermittent unsteadiness. Caloric testing demonstrated no response to ice water in the

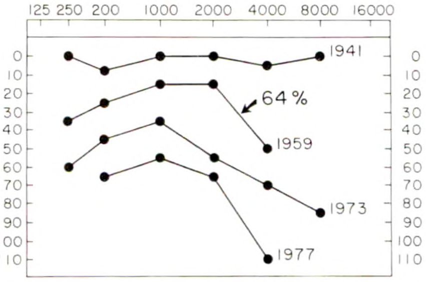

Fig. 2. Composite audiogram summarizing progressive right sensorineural hearing loss.

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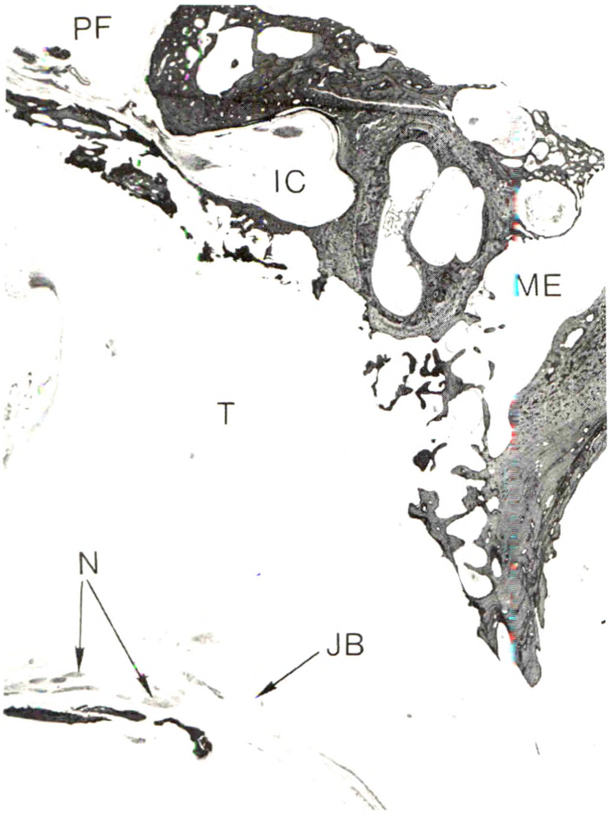

Fig. 3. Low power photomicrograph demonstrates tumor (T) at about the same level as shown radiographically in Fig. 1. There is compression of lumen of jugular bulb (JB). ME - Middle ear; N - Nerves in jugular foramen.

right ear and a normal response on the left. The patient died August 15, 1980, at the age of 84 years from arteriosclerotic heart disease. The right and left temporal bones were removed four hours after death and placed in Heidenhain-Susa fixative. Both temporal bones were processed in routine fashion for histological preparations. The right temporal bone was sectioned in a vertical plane transverse to the long axis of the petrous pyramid in order to demonstrate the relationship of the jugular foramen to the labyrinth while the left temporal bone was sectioned in the conventional horizontal plane. The left temporal bone was normal.

Right Temporal Bone. Examination of the right temporal bone revealed a pale-staining, relatively acellular neoplasm occupying the region of the jugular foramen and expanding the periosteal bone layer medially toward the posterior fossa and superiorly toward the labyrinth and the internal auditory canal (Fig. 3). The floor of the internal auditory canal was elevated, compressing the neural structures in the canal. The bony labyrinth was intact. The lumen of the jugular bulb was markedly compressed by the tumor but the other nerve structures in the jugular foramen appeared normal (Fig. 3). The tumor mass had a central area of necrosis and was permeated by a great number of vascular channels containing trapped red blood cells. The makeup of the tumor was primarily by spindle and ovoid shaped cell nuclei separated in many areas by collagenous and loose fibrous tissue. In the peripheral portion of the tumor, the cell nuclei displayed a tendency toward pallisading (Fig. 4). These histological features are consistent with a neurofibroma. It was not possible to identify the origin of the tumor. The margins of the tumor adjacent to the hypotympanum and the dura of the posterior cranial fossa showed retraction suggesting collapse or shrinkage of the tumor.

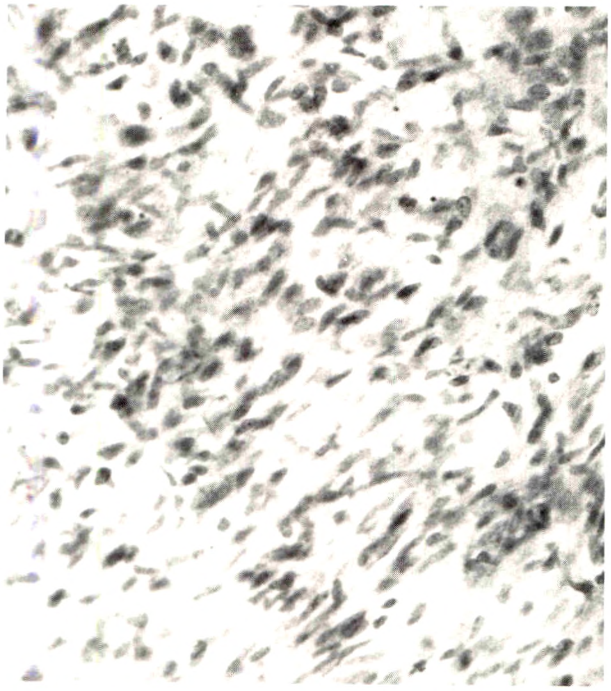

Fig. 4. High power photomicrograph taken from cellular areas of tumor. Spindle-shaped cell nuclei show tendency toward pallisading characteristic of neurofibroma.

Evaluation of the Labyrinth. The area of stenosis in the internal auditory canal occurred at the glial portion of the eighth nerve and there was almost complete degeneration of nerve fibers in the Schwann cell portion of the nerve to the bony labyrinth. There was almost total loss of spiral ganglion cells in Rosenthal's canal with only a few remaining ganglion cells devoid of processes (Fig. 5). Bundles of nerve fibers representing the efferent olivocochlear bundle were seen traveling tangentially in Rosenthal's canal (Fig. 6). The organ of Corti and accessory structures in all turns appeared normal.

The vestibular ganglion was almost totally degenerated with the remaining ganglion cells displaying a truncated appearance (Fig. 7). The bony channels in the labyrinth wall were almost devoid of nerve fibers with only small caliber nerve fibers scattered throughout (Fig. 8). The scattered appearance of these fibers is consistent with the distri-

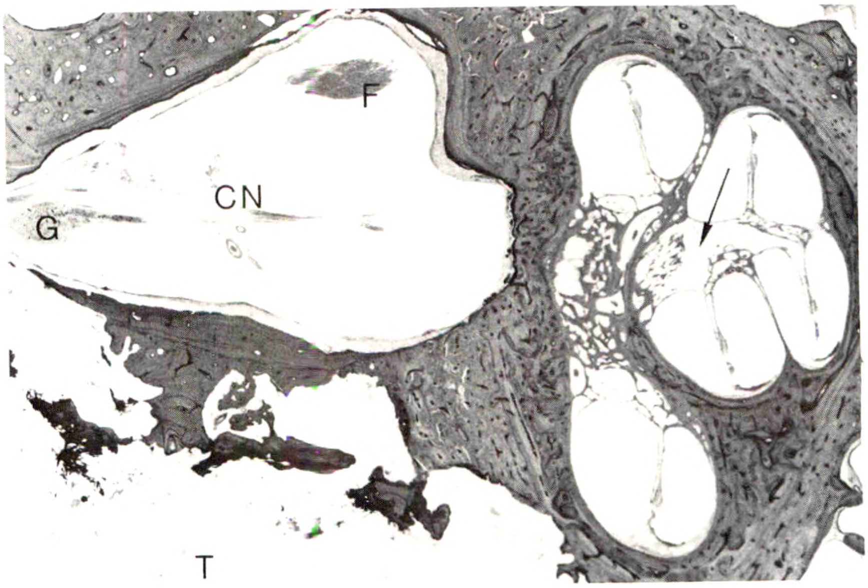

Fig. 5. Medium power photomicrograph shows atrophic cochlear nerve (CN) distal to compression of its glial segment (G) by tumor (T). There is complete loss of spiral ganglion cells (arrow) with normal organ of Corti.

bution of the efferent vestibular fiber pathway. All vestibular end-organs contained a normal complement of sensory and supporting cells (Fig. 9).

The facial nerve was compressed in the medial portion of the internal auditory canal with some disarray of nerve fibers just lateral to the point of narrowing. These fibers then formed a slightly smaller facial nerve in the distal portion of the internal auditory canal. The tympanic portion of the facial nerve showed a separation of several fascicles containing a slightly diminished number of facial nerve fibers. The vertical portion of the facial nerve consisted of a single fascicle with a normal density of sensory nerve fibers and a diminished number of motor axons (Fig. 10).

DISCUSSION

Clinical Presentation. The pathology of the tumor found in this temporal bone is consistent with a neurofibroma. Neurofibromas or schwannomas may arise anywhere in the body where myelinated nerve fibers exist. In the head and neck region, they are reported more frequently in the parapharyngeal space (cranial nerves IX, X, and sympathetic) and in the internal auditory canal from the eighth nerve.[8-10] Large schwannomas of the facial nerve often present as a middle ear neoplasm while small facial nerve tumors may only produce facial paralysis. However, neurofibromas or schwannomas arising from the nerves of the jugular foramen may form either a cerebellopontine angle tumor[11-13] or a tumor of the jugular foramen.[6,14]

Two cases of jugular foramen schwannoma presenting as a glomus jugulare tumor were reported in 1976.[6] This variety of schwannoma may mimic the glomus jugulare very closely both clinically and radiographically; tissue diagnosis is necessary for this differentiation. The present case report again demonstrates the similarity of the glomus jugulare tumor and neurofibroma arising from the jugular

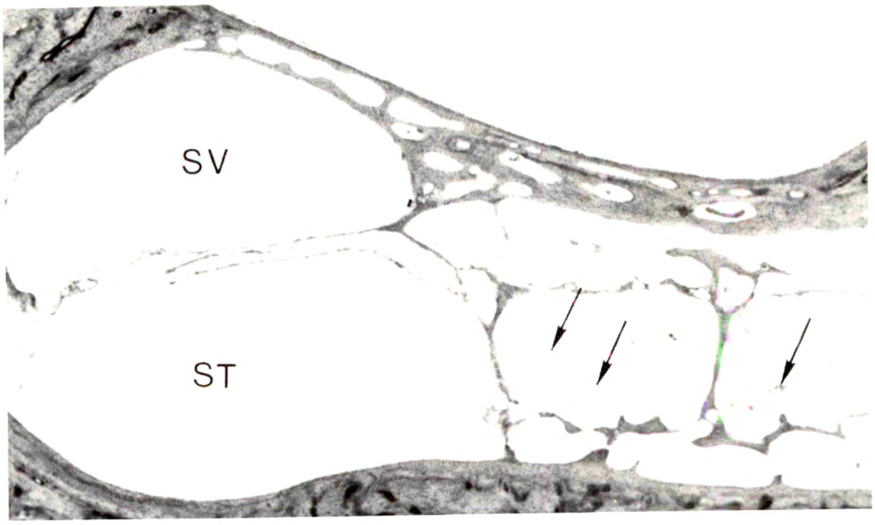

Fig. 6. Medium power view of cochlea shows tangentially coursing nerve fibers of olivocochlear bundle (arrows) in Rosenthal's canal which is devoid of ganglion cells. SV - Scala vestibuli; ST -Scala tympani.

Fig. 7. Scarpa's ganglion showing marked loss of vestibular ganglion cells and loss of neuronal processes.

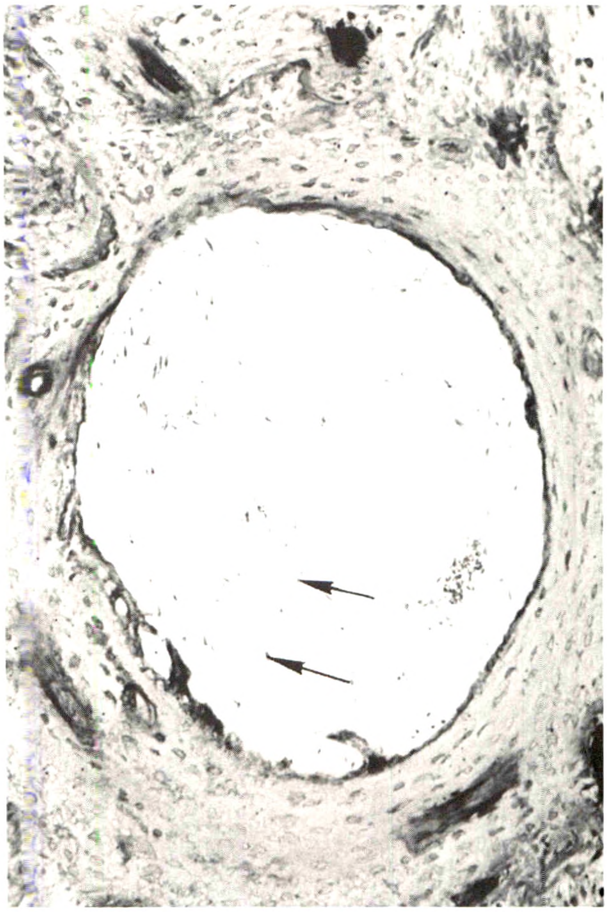

Fig. 8. Singular canal contained scattered small caliber vestibular nerve fibers (arrows).

foramen. The differentiation of these two lesions emphasizes the need for accurate diagnosis before treatment is recommended. The pathology of the neurofibroma in the present temporal bone specimen supports additional clinical and radiographic findings which may distinguish between these two neoplasms prior to biopsy. Although arteriography shows a vascular supply from the ascending pharyngeal artery to both tumors, there is a much richer flush with the glomus jugulare tumor. Collapse of the internal jugular vein secondary to compression of the jugular bulb by the neurofibroma has been noted surgically[6] as well as in the present temporal bone. On the other hand, in the presence of the glomus jugulare tumor, the internal jugular vein is usually of normal size or may be enlarged by intraluminal extension of a tumor mass. The diameter of the vein can be assessed during the venous phase of arteriography or by venography.

Pathology. Neurofibromas arising within the jugular foramen produce clinical defects by compression of the vascular and nervous structures in this region.[6,11-13] The early signs are produced by compression of the 9th, 10th and 11th cranial nerves in the foramen. Probably the most symptomatic of these is the tenth cranial nerve where voice change is usually the earliest clinical symptom. This was observed in the present case as the initial presenting symptom. Palatal weakness as a result of cranial nerve IX compression and atrophy of the sternocleidomastoid muscle as a result of paralysis of the 11th cranial nerve are not usually noticed until the paralysis has become complete. Central nervous system signs suggesting compression of the jugular bulb and collapse of the internal jugular vein are not observed because of venous flow through the contralateral sigmoid sinus.

Probably the most distressing clinical symptoms are related to involvement of the seventh and eighth cranial nerves because of compression of these nerves in the internal auditory canal or the cerebellopontine angle by an expanding tumor.[15] The present case demonstrates compression of the internal auditory canal as a result of displacement of the inferior wall by the expanding solid tumor mass. Arising in the jugular foramen, the tumor extended through areas of the temporal bone which offer the least resistance (bone marrow, air cells) and destroys the periosteal bone by compression. The bony labyrinth wall demonstrated its resistance to tumor compression or invasion, thereby protecting the labyrinth.

Neural Deficits. This temporal bone specimen demonstrates the response of sensory and motor neurons to the effect of a compressive lesion of the internal auditory canal. The site of compression of the eighth nerve was located in the glial segment

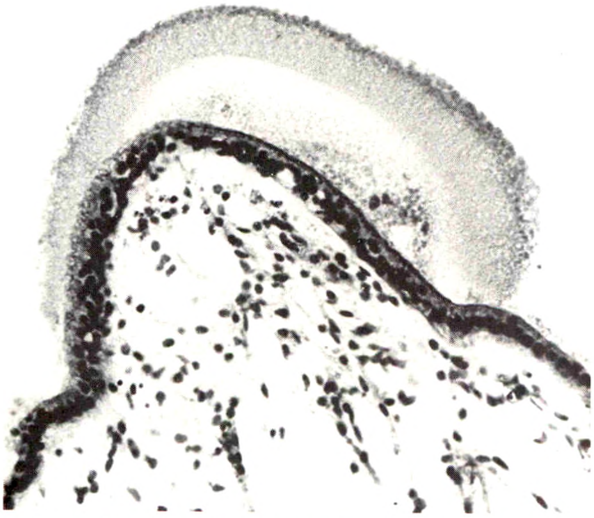

Fig. 9. Despite marked degeneration of vestibular nerve fibers, sense organs were normal as illustrated by crista ampullaris.

where the axons of the vestibular and cochlear bipolar neurons are located. The resulting retrograde degeneration with preservation of auditory and vestibular end-organs is typical of a neural or retrolabyrinthine lesion. It has long been known that primary cochlear neurons readily (within one month) undergo this reaction following injury to their axons or dendrites.[16] However, the vestibular bipolar neuron has been previously thought to resist such retrograde death. Experimental observations regarding this behavior of vestibular neurons have been based on survival times of one to several years. The long survival period of 57 years in this case suggests that a longer period may be necessary to evaluate the retrograde degeneration of vestibular neurons.

The clinical features of a progressive retrocochlear and retrovestibular lesion are well demonstrated in this case. The auditory deficit was characterized by a loss of speech discrimination out of proportion to the frequency threshold elevation. If speech testing had been performed in earlier hearing tests, it is likely that some loss of speech discrimination would have been detected which could account for the hearing loss noted prior to 1941. The rather equal threshold elevation of the frequency spectrum over a period of more than 20 years is also characteristic of a progressive loss of neurons in the cochlear nerve.

The vestibular symptoms resulting from a slow destructive process of the vestibular nerve ranged from slight unsteadiness to intermittent mild or moderate dizzy spells which were not incapacitating. Although there was no response to an ice water caloric stimulus in the right ear in 1959, the patient continued to experience dizziness and unsteadiness beyond that date. The combination of the presence of symptoms in the absence of vestibular function emphasizes the inadequacy of the caloric test as a complete indicator of labyrinth function. Otolith function as well as some neural supply to the cristae is not measured by the caloric stimulus.

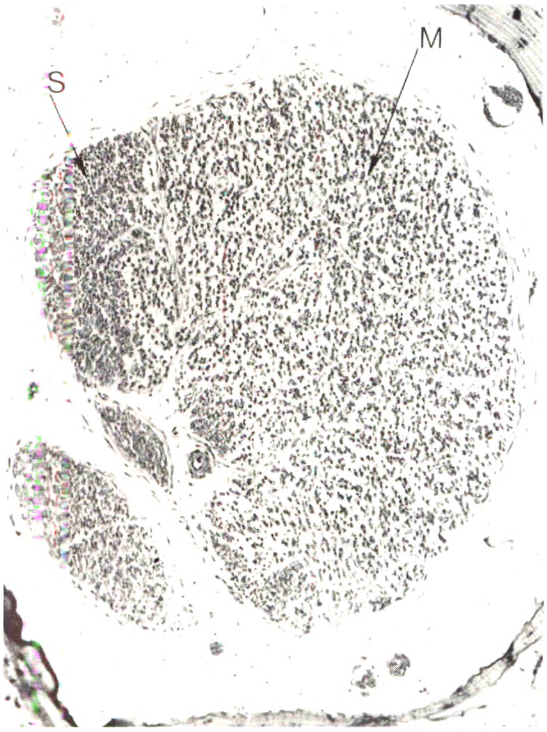

Fig. 10. Facial nerve near pyramidal bend showing slightly decreased number of motor axons (M) while nervus intermedius component (S) is normal.

Motor neurons are more resistant to compression and have a greater regenerative capacity. The efferent neurons to the cochlea and vestibular end-organs were preserved in this case. The small size and location of the remaining nerve fibers in this specimen are similar to the experimental demonstration of the efferent cochlear[17] and vestibular[18] systems. These observations support the conclusion that many of the peripheral axons present in this labyrinth belong to the human efferent labyrinth pathway. It is possible that these efferent neurons escaped significant compression because of their central location in the vestibular nerve trunk. However, it is also possible that they regenerated following compression in the internal auditory canal.

The facial nerve also demonstrated this behavior of motor neurons. Despite unrelieved compression sufficient to cause complete facial paralysis in this patient, there was excellent anatomical regeneration of the facial nerve axons beyond the point of compression (Fig. 10). The degree of facial muscle function depends on precise regeneration of axons to their previous regional muscle's end-plates. Since it is now conclusively shown that facial motor axons are intermixed throughout the entire temporal course of the facial nerve[19,20] it is inevitable that a disorganized, mass movement of facial muscles results from facial nerve regeneration.

Treatment. The treatment of glomus tumors and neurofibromas differs. Glomus tumors are treated surgically if possible and radiation therapy is reserved to manage residual tumor or those tumors that are nonresectible. It is believed that the radiation effect is on the small blood vessels rather than the tumor cells. Neurofibroma tumor cells (Schwann cells and fibroblasts) are believed not to be responsive to radiation therapy. Surgical excision has been the treatment of choice. However, radiation therapy may also reduce the size of a neurogenic tumor by its effect on small blood vessels. It is possible that the clinical improvement in the present case is explained by the histological appearance of a shrunken tumor with a central zone of cystic degeneration which may have resulted from a loss of blood supply. Of course, it is also possible that the tumor underwent a spontaneous degeneration unaffected by the radiation therapy. Finally, this case demonstrates that withholding surgical treatment of these tumors is consistent with a long and useful life.

REFERENCES

1. Rosenwasser H. Neoplasms involving the middle ear. Arch Otolaryngol 1940; 32:38-53.

2. Bradley WH, Maxwell JH. Neoplasms of the middle ear and mastoid. Report of fifty-four cases. Laryngoscope 1954; 64:533-56.

3. Goodman ML. Middle ear and mastoid neoplasms. Ann Otol Rhinol Laryngol 1971; 80:419-24.

4. Alford BR, Guilford FR. A comprehensive study of tumors of the glomus jugulare. Laryngoscope 1962; 72:765-87.

5. Valvasorri GE, Buckingham RA. Middle ear masses mimicking glomus tumors: radiographic and otoscopic recognition. Ann Otol Rhinol Laryngol 1974; 83:606-12.

6. Gacek RR. Schwannoma of the jugular foramen. Ann Otol Rhinol Laryngol 1976; 85:214-24.

7. Hoople GD. Personal experiences with glomus jugulare tumors. Trans Am Otol Soc 1964; 52:177-89.

8. Conley JJ. Neurogenous tumors in the neck. Arch Otolaryngol 1955; 61:167-80.

9. Putney FJ, Moran JJ, Thomas GK. Neurogenic tumors of the head and neck. Laryngoscope 1964; 74:1037-59.

10. Katz AD, Passy V, Kaplan L. Neurogenous neoplasms of major nerves of face and neck. Arch Surg 1971; 103:51-6.

11. Mountjoy L, Dolan K, McCabe B. Neurilemmoma of the ninth cranial nerve masquerading as an acoustic neuroma. Arch Otolaryngol 1974; 100:65-7.

12. Clemis J, Hoffsinger D, Derlacki E. A jugular foramen schwannoma simulating an acoustic tumor with recovery of retro-labyrinthine cochleovestibular function. Trans Am Acad Opthalmol Otolaryngol 1977; 84:686-96.

13. Clemis J. Neurogenic tumors of the skull base. Otolaryngol Head Neck Surg 1980; 88:511-8.

14. Neely JG. Reversible compression neuropathy of the eighth cranial nerve from a large jugular foramen schwannoma. Arch Otolaryngol 1979; 105:555-60.

15. Naunton R, Proctor L, Elpern B. The audiologic signs of ninth nerve neurinoma. Arch Otolaryngol 1968; 87:222-7.

16. Wittmaack K. Ueber sekundäre Degenerationen in inneren Ohre nach Akustikustammverletzungen. Verh Dtsch Otol Ges 1911; 20:289.

17. Gacek RR. The efferent cochlear bundle in man. Arch Otolaryngol 1961; 74:690-4.

18. Gacek RR, Nomura Y, Balogh K. Acetylcholinesterase activity in the efferent fibers of the stato-acoustic nerve. Acta Otolaryngol (Stock) 1965; 59:541-53.

19. Thomander L. The facial nerve complex. Anatomical and neurophysiological aspects. Acta Universitatis Upsaliensis 1981; 404:1-40.

20. Gacek RR, Radpour S. Fiber orientation of the facial nerve: An experimental study in the cat. Laryngoscope 1982; 92:547-56.

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AMERICAN CLEFT PALATE ASSOCIATION/AMERICAN CLEFT PALATE EDUCATIONAL FOUNDATION

The ACPA/ACPEF annual convention will be held May 4-7, 1983, at the Hyatt Regency in Indianapolis, Indiana. For further information contact Jane Angelone Graminski, Administrative Secretary, American Cleft Palate Association, American Cleft Palate Educational Foundation, 331 Salk Hall, University of Pittsburgh, Pittsburgh, PA 15261; (412) 681-9620.

Ann Otol Rhinol Laryngol 92:1983

TEMPORAL BONE FINDINGS IN CASES OF SALT WATER DROWNING

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The otologic literature contains no description of the histopathological features of temporal bones of persons who perished in drowning accidents. Three temporal bones from two fatal cases of drowning were studied in serial sections. Two temporal bones were from a man aged 31 years who collapsed after scuba diving and died three days later. One temporal bone was from a 32-year-old man, serving in the navy, who drove his car, probably accidentally, into the sea and drowned in it. Histopathological findings appeared to be similar in the two cases. Diffuse hemorrhage was evident throughout the middle ear and inner ear. The tympanic and round window membranes appeared to be intact although hemorrhage had occurred within the tissue layers of the membranes. This finding contrasts with observations of ruptured membranes by other investigators.

The ear can be seriously affected in drowning and diving accidents. Diving sequelae have been widely studied, but the otologic literature contains no reports on the histopathological findings in the temporal bones of persons who died in drowning accidents. Two relevant case studies are presented.

CASE REPORTS

Case 1. A 31-year-old man had been scuba diving approximately 30 to 40 minutes in about 4.5 to 9 m of water. On snorkeling to shore he was reported by his partner to have developed gasping respiration. At the shore he appeared to be cyanotic and pulseless. Mouth-to-mouth respiration was started, and his color improved. The ambulance arrived within ten minutes and resuscitation was started. He was taken to the San Pedro Peninsula Hospital where an esophagaeal airway was established. Both pupils were dilated and fixed and intubation produced coarse breath sounds. The heart action was regular. Neurological examination revealed absent reflexes and no response to pain stimulation. His blood pressure fluctuated, rising to between 50 and 130 mm/Hg. He died on the third day of hospitalization.

Case 2. A 32-year-old man returned to his unit at the Oakland Naval Base after dark and drove his car into the ocean. It was not possible to establish suicidal intent or intoxication. The car was found promptly, but the body was recovered considerably later some distance from the car.

HISTOPATHOLOGICAL FINDINGS

The temporal bones in this study were processed by the usual celloidin embedding procedure after decalcification. Sectioning was in the midmodiolar plane and every tenth section was stained with hematoxylin-eosin.

Case 1. In the right ear the external canal was free but blood was noted in the inner surface of the otherwise intact tympanic membrane and in all spaces of the tegmen containing a dilated subarcuate artery. Blood occupied the middle ear and the oval window. The shape of the inner ear was normal, but there was some hemorrhagic infiltration. The round window membrane was intact. The semicircular canals and the inner meatus contained blood and the dilated endolymphatic duct showed hemorrhagic infiltration.

In the left ear, all pneumatic spaces of the tegmen and of the middle ear were filled with mucous fluid and blood. The endolymphatic duct was dilated.

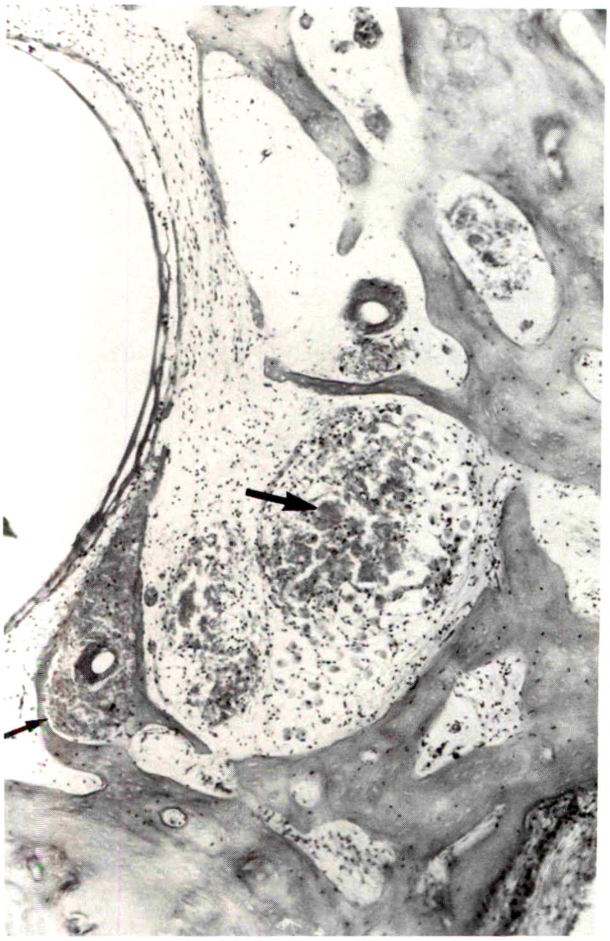

Fig. 1. Hemorrhage into modiolus. Extravasated blood can be seen among ganglion cells (large arrow) and around artery (small arrow). (H and E, x73)

From the House Ear Institute (Eccles Laboratory) and the Otologic Medical Group, Inc, and the University of Southern California School of Medicine, Los Angeles.

REPRINTS — George Kelemen, MD, House Ear Institute, 256 South Lake Street, Los Angeles, CA 90057.

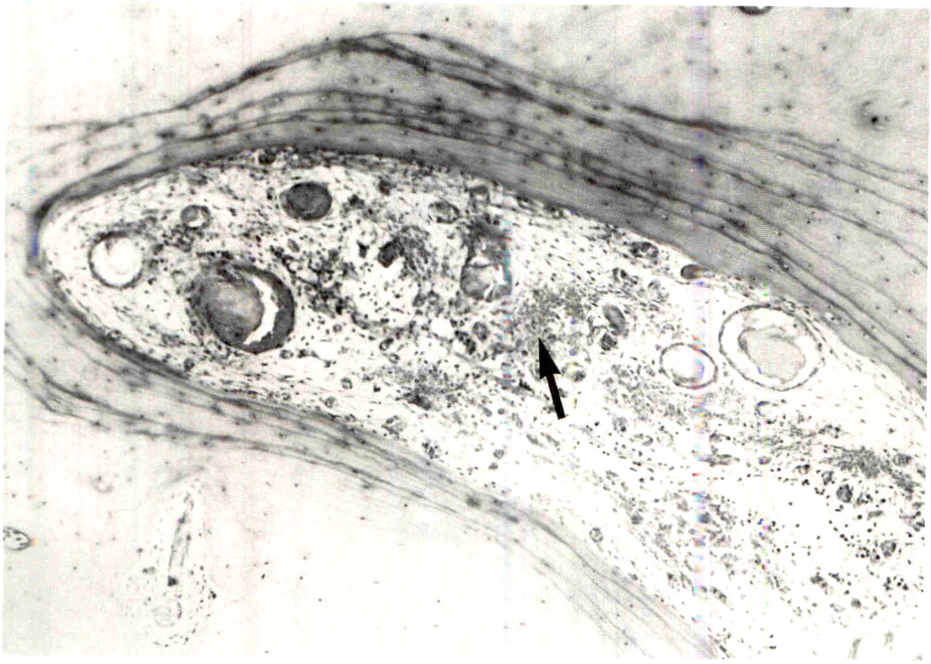

Fig. 2. Hemorrhage into mucosa of mastoid air cell (arrow). (H and E, x73)

The tympanic and round window membranes were preserved.

Case 2. All pneumatic spaces of the tegmen were filled with blood. Blood was noted within the intact tympanic membrane. The subarcuate artery was dilated. Blood surrounded the incudomalleal joint and all pneumatic spaces around the middle ear. The endolymphatic duct was dilated. In the inner ear, the Reissner membrane bulged into the apical scala media; otherwise the membrane was straight. The congested vascular stria was detached from the bony wall. The macula sacculi were also detached from the bony wall. Blood was found in the endolymphatic sac near the vestibular aqueduct. The round window membrane was intact. Blood was also present in the internal meatus.

In summary, both cases showed evidence of hemorrhage in the middle ear space and in the inner ear; in case 2 blood was seen in the external ear also. Both round and oval window membranes were hemorrhagic but intact in these cases.

The right sides in both cases 1 and 2 were basically identical. The left sides varied, with case 1 showing evidence of probable serous panotitis. This condition may have blocked the hemorrhaging.

DISCUSSION

Hemorrhage has been recognized as the principal pathological finding in drownings reported in the literature as well as in these cases.[1-7] Farmer et al[2] noted the perilymphatic space of the inner ear was hemorrhagic after diving. The pathogenesis of these cases is related to air bubbles blocking capillary circulation and resulting in hemorrhage when the capillary walls begin to leak.

Whether this mechanism operates in drowning accidents cannot be accurately ascertained. The apparent panotitis on the left side in case 1 may have played some role in the process. It is most interesting to note that, in contrast to some reports, neither the tympanic nor the round window membrane was ruptured although bleeding occurred within the layers of these membranes.[8-13] Schuknecht[12] mentioned the possibility of round window damage during scuba diving. Miriszlai and Sandor[11] noted that perilymphatic fluid pressure increased around the ruptured round window membrane in experimental cats.

The significant histopathology in the two cases presented is in the middle ear and mastoid. Figures 1 and 2 illustrate that gross hemotympanum, but not necessarily membrane rupture, are pathognomonic for drowning.

ACKNOWLEDGMENT — Thanks are due to Lt Keith M. Reynolds, MC, USN, for providing the temporal bone of case 2 and to Janetta Paladini for the preparation of this manuscript.

REFERENCES

1. Beasley JW. Inner ear damage due to barotrauma. Wis Med J 1974; 73:5143-5.

2. Farmer JC, Thomas WG, Youngblood DG, Bennett PB. Inner ear decompression sickness. Laryngoscope 1976; 86: 1315-27.

3. Freeman P, Edmonds C. Inner ear barotrauma. Arch Otolaryngol 1972; 95:556-63.

4. Goodhill V. Inner ear barotrauma. Letter to the editor. Arch Otolaryngol 1972; 95:488.

5. Goodhill V. Ear diseases, deafness, and dizziness. Hagerstown: Harper & Row, 1979.

6. Luke CG. Spray-tish for scuba-divers. Med J Aust 1975; 2:407.

7. Paparella MM. Barotrauma (aerotitis). In: Paparella MM, Shumrick DA, eds. Otolaryngology: the ear. Vol 2. Philadephia: WB Saunders, 1980:1429-31.

8. Freeman P, Tonkin J, Edmonds C. Rupture of the round window membrane in inner ear barotrauma. Arch Otolaryngol 1974; 99:437-42.

9. Goycoolea MC, Paparella MM, Juhn SK, Carpenter AM. Oval and round window changes in otitis media: potential pathways between middle and inner ear. Laryngoscope 1980; 90:1387-91.

10. Leek JH, Riess RL. Traumatic sudden deafness or a scuba diver gets it — in the ear. Minn Med 1973; 56:608-10.

11. Miriszlai E, Sandor P. Investigations on the critical perilymphatic pressure value causing round window membrane rupture in anesthetized cats. Acta Otolaryngol (Stockh) 1980; 89:323-9.

12. Schuknecht HF. Pathology of the ear. Cambridge: Harvard University Press, 1974.

13. Tonkin JP, Fagen P. Rupture of the round window membrane. J Laryngol Otol 1975; 89:733-56.

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NINCDS NOTES*

NEW NINCDS DIRECTOR APPOINTED

Dr. Murray Goldstein, an assistant surgeon general in the Public Health Service, has been named Director of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). National Institutes of Health Director Dr. James B. Wyngaarden announced the appointment on December 23, making Dr. Goldstein the Institute's fifth director since its establishment in 1950.

Dr. Goldstein has been acting director of NINCDS since February 1981. In a 23-year career with the Institute, he also served as NINCDS deputy director (1978-1981); director, Stroke and Trauma Program (1976-1978); director, Extramural Program (1961-1976); and chief, Special Projects Branch (1960-1961).

NINCDS TO HOLD CONFERENCE ON RESEARCH ISSUES IN POSITRON EMISSION TOMOGRAPHY

The National Institute of Neurological and Communicative Disorders and Stroke will sponsor a scientific conference on research issues in positron emission tomography, to be held at the National Institutes of Health, Bethesda, Maryland, June 16-17, 1983.

Participants will explore future trends in applying PET to the study of neurological disorders. New and unpublished data will be presented. The conference will provide a forum for identifying problems that limit progress in PET research, and for considering possible solutions. Sessions will focus on three main topics: technical aspects of isotope synthesis and imaging; definition of normal functions by PET; and evaluation of abnormal and diseased states.

Michael D. Walker, MD, director of the NINCDS Stroke and Trauma Program, is conference chairman. Chairing the three scientific sessions are Martin Reivich, MD, University of Pennsylvania Hospital, Philadelphia, Pa; Alfred Wolf, PhD, Associated University, Brookhaven National Laboratory, Upton, NY; and Henry Wagner, MD, Johns Hopkins University, Baltimore, Md.

Further information and advance registration forms are available from Zekin Shakhashiri, MD, Office of Planning and Analysis, NINCDS, Bldg. 31, Room 8A-03, Bethesda, MD 20205.

NEW STUDY QUESTIONS EAR DISEASE TREATMENT

A recent study has found that decongestant and antihistamine compounds, one of the most popular drug treatments prescribed for otitis media with effusion (secretory otitis media), are no more effective than a placebo. The drug treatment also causes significantly more side effects than the placebo, primarily mild sedation and weakness.

Dr. Charles D. Bluestone and associates at the University of Pittsburgh conducted the study under a contract from the National Institute of Neurological and Communicative Disorders and Stroke. The 3-year, double-blind, randomized trial evaluated a combination of an oral decongestant (pseudoephedrine hydrochloride) and antihistamine (chlorpheniramine maleate). The drugs, either separately or in combination, are widely prescribed, as well as being available without prescription in drugstores.

In the study, 553 infants and children who had otitis media with effusion completed a 4-week course of either decongestant-antihistamine therapy or a placebo. Of 278 patients treated with the drug, only 69 (about 25%) had no otitis media in either ear after 4 weeks of treatment. The 275 children who received the placebo had nearly identical results: 67 (about 24%) with no otitis media in either ear. Neither the age of the children nor the length of time they had otitis media affected the trial results.

The investigators conclude that oral decongestant-antihistamine combinations "do not appear to be indicated for the treatment of otitis media with effusion in infants and children." Results of the study were published in the *New England Journal of Medicine* 1983; 308(6)297-301.

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*This information is prepared monthly by the Office of Scientific and Health Reports, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Building 31, Room A806, Bethesda MD 20205; (301) 496-5924.

Ann Otol Rhinol Laryngol 92:1983

NASOPHARYNGEAL MASSES IN ADULTS

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BOSTON, MASSACHUSETTS

Nasopharyngeal masses in adults present a perplexing problem because of the concern for malignancy. A retrospective review of the records, radiographs and biopsy histology of 57 patients presenting in one year with nasopharyngeal masses at the Massachusetts Eye and Ear Infirmary suggests that persistent pain, epistaxis, trismus, or cervical mass are uncommon in patients with benign histology and should alert the clinician to the probability of malignancy. A high index of suspicion on the part of the clinician is essential for the successful recognition of early lesions. The roles of conventional radiography, polytomography, and computed tomography scans are discussed. Patients with malignant lesions are contrasted with those having benign lesions.

INTRODUCTION

The poor prognosis for patients with nasopharyngeal carcinoma (NPC) is principally due to its advanced stage at the time of diagnosis. In an effort to gain further insight into the diagnostic problems posed by nasopharyngeal masses in adults, the charts and radiologic studies of all patients hospitalized for possible nasopharyngeal malignancies at the Massachusetts Eye and Ear Infirmary in 1978 were reviewed. This year was arbitrarily selected to provide a sampling of our current experience with nasopharyngeal masses and more specifically with nasopharyngeal malignancies. Of the 57 patients studied, all had nasopharyngeal biopsies with histologic examinations. The 37 patients with benign lesions and the 20 patients with malignant lesions were contrasted for distinctive clinical and radiologic findings that might lead to the earlier detection of NPC. Techniques of biopsy, tissue handling and histological considerations important for the successful diagnosis of NPC are reviewed.

METHODS

The medical records, radiologic studies, and histologic slides of 57 patients seen at the Massachusetts Eye and Ear Infirmary in 1978 with suspected nasopharyngeal malignancies were reviewed. Excluded from the study were patients with an established diagnosis of nasopharyngeal carcinoma, adenoiditis, and juvenile angiofibroma. Data included presenting symptoms, interval to diagnosis, physical findings, stage of neoplasm at presentation, histologic diagnosis, response to treatment, and results of radiologic studies.

The radiologic examinations included lateral and basal views of the nasopharynx, frontal and lateral pluridirectional tomograms, and computed tomography (CT). The nasopharyngeal thickness was compared on lateral films. The posterior wall soft tissue thickness was determined on a plane extending from the posterior edge of the soft palate to the anterior lip of the foramen magnum. The roof soft tissue thickness was measured on a plane extending from the skull base along the posterior pterygoid margin to the posterior edge of the hard palate.

All biopsies were performed under general anesthesia in a major operating room suite. There were no recorded operative or postoperative complications.

RESULTS

The presenting symptoms in this study are depicted in Table 1. In both groups, serous otitis media was the most common complaint. Nasopharyngeal symptoms and pain were more frequently seen in the malignant cases. Bleeding and trismus were present exclusively in the malignant group. There were no patients with cranial neuropathies in this series. Cervical masses were among the presenting symptoms in 7 of 37 of the benign patients and in 9 of 20 of the malignant patients. In the benign group, four of these seven neck masses proved to be malignant processes unrelated to nasopharyngeal carcinoma, emphasizing the concept that neck masses in adults are malignancies until proven otherwise.

In patients with malignant disease, serous otitis media was the most frequent earliest presenting symptom followed by nasopharyngeal obstruction, pain, and bleeding. Although 9 of 20 patients had cervical metastases by the time of diagnosis, this was the earliest presenting symptom in only one patient.

The time interval from presenting symptoms to histologic diagnosis varied in the benign cases from two weeks to two years. The mean interval to diagnosis in the malignant group was seven months (range 3-18 months). In 5 of 17 patients, the interval to diagnosis exceeded 12 months. In this group, four had either invasion of the skull base or cervical metastases at the time of diagnosis.

Five patients in the benign group who lacked nasopharyngeal masses had biopsies because of symptoms of serous otitis media or cervical masses. Six patients had clinical masses unconfirmed by x-ray studies. In the malignant group, all patients had

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TABLE 1. PRESENTING SYMPTOMS IN BENIGN AND MALIGNANT GROUPS

	Complaints		*Earliest Findings*
	Benign Group	*Malignant Group*	*Malignant Group*
Nasopharyngeal			
Obstruction	5	9	5
Bleeding	0	5	2
Otologic (SOM)*	21	12	8
Ophthalmoneurologic	0	0	0
Cervical			
Mass	7	9	
Metastasis			1
Pain	5	9	4
No symptoms	3	0	—

*Secretory otitis media

nasopharyngeal masses and all but two had radiographic confirmation.

The clinical stage of the primary lesion and the distribution of cervical metastases of the malignant cases in this series are depicted in Table 2.

Radiographs were available for review in 53 of the 57 patients. All patients had lateral and basal survey views. Polytomes were performed in all of the malignant cases and in all but ten of the benign cases. Four of the malignant cases had CT examinations on a newly acquired body scanner. The measurements of nasopharyngeal soft tissue thickness show a similar distribution in both the benign and malignant groups as depicted in Table 3. Neither the thickness nor the mucosal profile of the nasopharynx on the lateral films was predictive of malignancy. Skull base erosion, hinted at on basal plain films and usually not seen on the lateral projections, was well defined by pluridirectional tomography. CT examinations demonstrated the tumors prior to definitive biopsy in three patients. In a fourth patient, CT was used to follow the progression of disease and accurately demonstrated extension into the eustachian tube and cranium.

PATHOLOGY

Histopathologic classification of malignant tumors of the nasopharynx used in this series includes squamous cell carcinoma, keratinizing; squamous cell carcinoma, nonkeratinizing; undifferentiated carcinoma (lymphoepitheliomatous type), and malignant lymphoma (WHO classification). The biopsy results of the 57 cases are shown in Table 4.

TABLE 2. CLASSIFICATION OF MALIGNANCIES

*Primary Site**	*No.*	*Nodal Involvement*	*No.*
T_1	2	Unilateral	5
T_2	6	Bilateral	3
T_3	2	Contralateral	1
T_4	10		
Total	20	Total	9

*American Joint Committee for Staging and End-Result Reporting, 1978.

TABLE 3. THICKNESS OF NASOPHARYNGEAL ROOF AND POSTERIOR WALL

Group	*Mean (mm)*	*Range (mm)*
Roof		
Benign group	12	4-27
Malignant group	14	6-35
Posterior wall		
Benign group	25	10-42
Malignant group	27	18-42

The spectrum of malignant disease occurred in the expected pattern of frequency. The majority of patients with benign histological lesions showed inflammatory changes or lymphoid hyperplasia.

CLINICAL COURSE

All the patients with malignancies were treated primarily with curative radiotherapy, usually a combination of external beam and local nasopharyngeal irradiation. In one case, a lateral rhinotomy and medial maxillectomy were performed prior to irradiation. There were no neck dissections.

Two-year follow-up results available in all 20 of the patients with malignancy are depicted in Table 5. Sixty percent of the patients have either died of their malignancies or experienced recurrences. Of those patients without evidence of disease at two years, two were clinically staged at the primary site as T4 and one as T3 and are, therefore, at high risk for recurrence.

The following case report from this series illustrates the problems that may arise in establishing a diagnosis of nasopharyngeal malignancy.

CASE REPORT

A 26-year-old male with no previous ear, nose or throat problems developed right otalgia and fullness following descent in an airplane in September 1977. In October, he developed pain in his right eye. Ophthalmologic evaluation was normal. By November, trismus accompanied increasing right eye and right ear pain, but visual fields remained normal. He was seen by an otolaryngologist who diagnosed serous otitis media. Treatment regimen included penicillin, dexbrompheniramine maleate (Drixoral), and codeine. A neurological consultation was obtained in December because of continued pain. The neurological examination and a head scan were normal. Later in December, a hearing loss developed in the

TABLE 4. PATHOLOGIC FINDINGS (MASSACHUSETTS EYE AND EAR INSTITUTE SERIES 1978)

		No. of Patients
Malignant		
Squamous cell carcinoma		7
Undifferentiated carcinoma, lymphoepitheliomatous type		10
Malignant lymphoma		3
	Total	20
Benign		
Chronic inflammation		24
Lymphoid hyperplasia		7
Mucous retention cyst		2
Tornwaldt cyst		1
Choanal polyp		1
Normal		2
	Total	37

TABLE 5. RESULTS OF TREATMENT (TWO-YEAR FOLLOW-UP)

Classification at Time of Diagnosis	*No.*	*Patients Died*	*Recurrence*	*NED**
T1	2	—	—	2
T2	6	—	3	3
T3	2	1	—	1
T4	10	4	4	2
Totals	20	5	7	8

*No evidence of disease

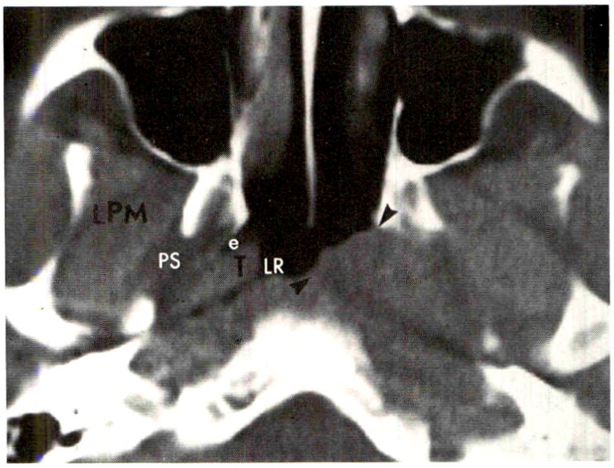
right ear, and a second otolaryngologist diagnosed serous otitis media. Decongestants were used for treatment. In January 1978, he was hospitalized and jointly evaluated by neurology, otolaryngology and oral surgery. The diagnosis was right temporomandibular joint syndrome and treatment consisted of codeine, methocarbamol (Robaxin), jaw exercises, and heat. In February 1978, he was seen at the Massachusetts Eye and Ear Infirmary because of persistent pain, trismus, hearing loss, and a 11.25 kg weight loss. Examination revealed serous otitis media of the right ear, trismus, and a granular mass in the nasopharynx on the posterior lip of the torus tubarius. A nasopharyngogram and conventional and pluridirectional nasopharyngeal x-ray studies were interpreted as normal. Temporal bone polytomography confirmed serous otitis media in the right tympanic cavity and mastoid. A temporomandibular joint study showed limitation of right condylar motion. A CT scan of the nasopharynx with contrast enhancement showed asymmetry of the nasopharyngeal air shadow with soft tissue encroachment in the region of the right torus tubarius and obliteration of the fat plane defining the right lateral pterygoid muscle (see figure). (These findings would explain the trismus.) There was a suggestion of bony erosion near the foramen lacerum on the right side. In March 1978, six months after the onset of symptoms, nasopharyngeal biopsies were obtained revealing undifferentiated carcinoma, lymphoepitheliomatous type.

This case illustrates a number of important features: 1) complaints of pain, especially trismus, associated with serous otitis media cannot be ignored; 2) the nasopharynx must be thoroughly examined in patients presenting with serous otitis media or atypical pain; 3) a head scan does not routinely include the nasopharynx; 4) plain films and polytomography can miss early nasopharyngeal lesions; and 5) computerized tomography can be most useful in accurately defining the extent of the lesion.

DISCUSSION

The presenting symptoms of the benign and malignant patient groups reveal several features worthy of note. Serous otitis media was the most common presenting symptom in both groups. A history of epistaxis or bloody discharge was indicative of malignancy since it was not seen in patients with benign lesions. Pain was present in both groups, but was proportionately more frequent in the malignant group. It was the original complaint in 25% of these patients. In the patients with malignancy, serous otitis media was the earliest presenting symptom encountered, followed by complaints of nasopharyngeal obstruction and bleeding.

In 25% of the patients with malignancy (5 of 17), the interval from initial symptom to diagnosis exceeded 12 months. Cervical lymph node metastasis was present in 9 of the 20 patients with malignancy but this was a presenting complaint in only one patient. The cervical metastasis, in most cases, developed some time after the patient's initial complaint.



Axial CT nasopharynx. Soft tissue thickening of the right posterolateral wall obliterates the right lateral pharyngeal recess (LR), the torus tubarius (T), and adjacent eustachian tube margins (arrow heads). The right paranasopharyngeal fibrofatty plane, seen as a low-density area on the normal side, is effaced by tumor. There is some thickening of the lateral pterygoid muscle. PS - Paranasopharyngeal space; e - Eustachian tube; LPM - Lateral pterygoid muscle.

Interestingly, cranial neuropathies, a frequent presenting symptom in most studies of nasopharyngeal carcinoma, were not seen in this series.

This study demonstrates the limitations of conventional radiographs in distinguishing between benign and malignant nasopharyngeal masses. Measurements of soft tissue thickness on radiographs did not distinguish between benign and malignant masses. Radiographs, however, can provide valuable confirmation of the presence of a mass and bone erosion in advanced disease. They are important as survey views for planning tomography. Polytomography and CT scans are helpful in the accurate staging of nasopharyngeal malignancies by defining the presence or absence of bony changes in the skull base. Malignant lesions staged as T4 erode the base of the skull (American Joint Committee). In Fletcher's series,[1] only one of the patients with nasopharyngeal malignancies eroding the skull base was salvaged by any form of treatment. Accurate staging in each individual case is imperative for the proper selection of treatment.

Computerized tomography promises to be our most sensitive technique for evaluating nasopharyngeal masses and should be performed, when available, on all patients with suspected or proven malignancies. The modern body scanners demonstrate the nasopharynx in unparalleled detail in both coronal and horizontal planes.[2,3] Newly available software permits data reconstruction of sagittal and oblique projections. By defining soft tissue structures, CT now makes it possible to see the relationship of tumor to mucosal surfaces and musculofacial planes. Orbital and sinus extension and alterations in bone are readily appreciated. Contrast enhancement aids in the differential diagnosis by demonstrating tumor vascularity, intracranial extension, vascular encroachment and nodal involvement. A clinician ordering CT scans of the nasopharynx should be aware that it cannot be demonstrated on the older head scanners since the skull base is the lowest scanning plane. A brain scan on any unit does not routinely include the nasopharynx. Although special positioning may demonstrate the nasopharynx on the most recent models of scanners, the study is probably best done on a body scanner. The nasopharynx should be clearly indicated as the area of concern and the radiologist should receive a pertinent history.

The clinician must remember that the differentiation between benign and malignant nasopharyngeal masses depends upon histological examination, and therefore, accurate biopsy techniques are essential. Transnasal biopsies using topical anesthesia invite inadequate sampling of tissue with resultant delay in diagnosis. The most common location for NPC is on the lateral wall of the nasopharynx either on the torus tubarius or in the fossa of Rosenmüller. The roof and superior posterior wall of the nasopharynx are also frequent sites of involvement. Biopsies of the nasopharynx should include tissue samples from within 1 cm of the torus tubarius if obvious tumor masses are not present.

In considering malignancies of the nasopharynx, it is important to communicate the clinical problems to the pathologist so that optimal handling of the specimen as to fixative and special studies can be performed. Frequently the histological alterations separating large cell lymphoma from undifferentiated carcinoma are difficult to establish unequivocally. Therefore, if lymphoma is the primary consideration, the tissue should be submitted fresh for immunoglobulin cell surface makers. Electron microscopic studies require immediate tissue fixation in glutaraldehyde or similar fixative. Tissue should always be handled delicately to avoid artifact.

Although not studied in this series, elevated Epstein-Barr (EB) virus antibody titers have been observed in cases of NPC, especially the lymphoepitheliomatous type.[4] Elevated EB antibody titers may be helpful in excluding a diagnosis of lymphoma except, of course, in cases of Burkitt's lymphoma. Studies are in progress to evaluate the EB antibody titers in NPC patients with active and controlled diseases which may reflect tumor response to therapy and tumor recurrence. Infectious mononucleosis can microscopically simulate lymphoma, especially Hodgkin disease. At least one case has been referred to this institution for radiation simulation in which review of the slides demonstrated a benign process consistent with mononucleosis.

Results of treatment of patients with nasopharyngeal malignancies is poor largely due to the advanced stage of disease at the time of presentation. Fletcher[1] reported an overall absolute 5-year survival for squamous cell carcinoma and lymphoepithelioma of the nasopharynx to be 35 to 40%. In cases with unilateral node involvement, the 5-year survival was 45%, and with bilateral nodes it was 30%. Wang[5] reported the results of irradiation in 170 patients with nasopharyngeal carcinoma. The overall 5-year survival was 39%. Lederman,[6] in an earlier series, showed a 50% survival at two years which fell to 13% by five years. Shanmugaratnam et al[7] in a recent review of 363 cases of NPC from Singapore, reported an overall survival of 25.3% following treatment with radiotherapy. Wang[5] reported 10 of 58 T4 patients alive without evidence of disease five years following treatment. In our series, 25% of the patients with malignancies have expired and another 35% have experienced recurrences at two years of follow-up (Table 4).

CONCLUSION

The early detection of nasopharyngeal malignancy continues to challenge the clinician. Early recognition and treatment favorably influence survival. Complaints of pain, epistaxis, trismus, or cervical mass are uncommon in the patients with benign lesions and should alert the clinician to the probability of malignancy. The interval to diagnosis in this series exceeded 12 months in a significant number of patients with malignancies, underscoring the limitation of current techniques in establishing early diagnoses. Polytomography and CT studies are recommended when nasopharyngeal malignancy is suspected or diagnosed. A high index of suspicion on the part of the clinician remains the best safeguard against misdiagnosis. Clinical symptoms suggestive of malignancy demand prompt and conclusive evaluation.

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REFERENCES

1. Fletcher GH, MacComb WS. Cancer of the head and neck. Baltimore: Williams and Wilkins, 1967.

2. Bohman L, Mancuso A, Thompson J, Hanafee W. CT approach to benign nasopharyngeal masses. AJR 1981; 36:173-80.

3. Mancuso A, Bohman L, Hanafee W, Maxwell D. Computed tomography of the nasopharynx: normal and variants of normal. Radiology 1980; 137:113-21.

4. Neel BH III, Pearson GR, Weiland LH, et al. Anti-EBV serologic tests for nasopharyngeal carcinoma. Laryngoscope 1980; 90:1981-90.

5. Wang CC, Meyer JE. Radiotherapeutic management of carcinoma of the nasopharynx. Cancer 1971; 28:566-70.

6. Lederman M. Cancer of the nasopharynx. Springfield Ill: Charles C Thomas, 1961.

7. Shanmugaratnam K, Chan SH. Histopathology of nasopharyngeal carcinoma. Cancer 1979; 44:1029-44.

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VOCAL FATIGUE

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The phenomenon of vocal fatigue, although not well understood, is commonly considered a symptom of voice misuse. This paper reviews the clinical and experimental evidence linking vocal fatigue to the quality, pitch, and loudness of voice use. Other reasons for voice change are discussed. The paper concludes by stressing the immediate clinical benefits of voice endurance testing as well as its potential experimental contribution to a better scientific understanding of optimum and abusive vocal behavior.

FATIGUE AND VOICE QUALITY

Fortunately, our tongues and soft palates are usually spared the symptoms of vocal overwork that so commonly afflict the larynx. Of all the organs used for speaking, the larynx is unique in its susceptibility to both heard and felt fatigue.

When the voice tires quickly, incorrect or at least injudicious vocal habits are usually said to be the cause. Although such an inference is strongly suggested in clinical encounter, a firm association between vocal fatigue and specific, presumably abusive phonatory styles has yet to be scientifically demonstrated. Indeed, research on vocal misuse has scarcely progressed beyond the accumulation of observations and case studies assembled 70 years ago by Moure and Bouyer.[1]

Investigating whether specific voice qualities are in fact fatiguing or abusive to the voice is more complex than it may seem. Agreement on how voice qualities are to be labeled is conspicuously lacking. And phonatory mechanisms may be dissimilar even when two voices appear perceptually alike. For example, Koike and von Leden[2] write that normal subjects cannot, strictly speaking, "simulate pathological initiations because the physical condition of the diseased larynx differs in essential respects from the normal larynx."

To elaborate further, a raspy voice may emanate from an abnormal larynx. The quality is deviant but not necessarily abusive to the mechanism that produced it. However, when the same voice quality is simulated (as in acting) by someone with usually normal voice, risks of laryngeal strain emerge since the muscle forces needed to simulate the disorder differ from those operating in the deviant mechanism. Ironically, the opposite also holds: efforts to simulate a normal voice without a corresponding improvement in physical condition (as with nodules or laryngitis) may actually increase laryngeal strain.

There are numerous anecdotal reports of fatigue or abuse associated with the deliberate imitation of voice quality disorders. Blakeley,[3] a speech pathologist, felt that his classroom imitations of voice disorders were the most to blame for his vocal trauma (bilateral cord edema) and the consequent hoarseness that persisted for three months. Actors with usually vigorous voices unexpectedly encounter similar discomforts and vocal symptoms when they assume a strained rough phonatory style for character portrayal.

The lack of physiologic correspondence between natural and simulated voice abnormality may explain some apparent literature contradictions. After they had agreed to simulate a tense harsh voice, three normal subjects observed by Brackett[4] showed clear evidence of fold inflammation within 5 to 15 minutes of talking. In contrast, Sherman and Jensen[5] found that persons with normally (habitually) harsh voices showed no general evidence of vocal fatigue — even after 90 minutes of continuous oral reading. Along much the same line, Moore[6] writes that "a unilateral contact ulcer is known to have developed following a single two-minute period of (deliberate) low pitched grunting phonation that was associated with repetitive contact between the arytenoid cartilages." The other side to this story is that spastic dysphonics by all reports remain surprisingly free of serious hemorrhages or ulcerations despite their habitually tense, hyperadducted phonatory styles.

FATIGUE AND VOCAL PITCH

Judgments of speaking pitch bear an imperfect relationship to speaking fundamental frequency.[7] Loudness, strictly speaking, should also be differentiated from intensity or sound pressure level. For ease of expression, however, we take the liberty of using these perceptual and acoustic terms interchangeably, intending only their acoustic meaning.

Speaking pitch is usually cited as a factor in vocal fatigue and voice disorder. A superficial reading of published electromyographic laryngeal research suggests a rather straightforward relationship be-

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tween voice fundamental frequency and the degree of longitudinal vocal fold tension: as pitch rises, the sum of thyroarytenoid and cricothyroid muscle activity increases. Are the lowest vocal pitches, then, always the most hygienic, the least fatiguing in the muscular sense? Not at all, but there is also no reason for avoiding them entirely. At phrase endings, for example, even superior speakers lapse into pitches lower than any they can musically sustain;[8] here, the fold vibrations often slow down mainly because subglottal air pressure decreases, hardly a phenomenon to be thought of as abusive or even tiring to the larynx.

But while low pitches may be produced without laryngeal strain, it is obvious that they need not be. An increase in isotonic vocal muscle activity, for example, will lower rather than raise pitch.[9] It is thus useful to view voice fundamental frequency as an outcome that may or may not involve changes in the activity of numerous specific muscles.[10] Adjustments related to the outcomes of quality and especially intensity undoubtedly play important superimposed roles.

It is, for instance, difficult to achieve strong voice at the lowest end of the phonational frequency range. A voice pitched at its lowest becomes particularly vulnerable to strain with attempts at loud voice because the burden of speaking louder near the frequency range bottom, unlike at higher pitches, falls mainly on the laryngeal muscles regulating glottal resistance.[11] These muscles alone can only raise subglottal pressure so much through glottal resistance. If the respiratory muscles bolster the airflow, subglottal pressure and hence vocal intensity can of course be further increased, but then the rate of fold vibration will usually also quicken. In line with this thinking, Coleman and colleagues[12] demonstrated that the maximum vowel intensity achievable by normal subjects increased as fundamental frequency was allowed to rise within the modal register.

As a conservative rule of thumb for deciding upon a least fatiguing target speaking pitch, Perkins[13] concludes that pitch interacts with constriction in untrained voices at points both above and below the lower midpoint range. Others are less cautious in their generalizations. Cooper,[14(p77)] for example, unhesitatingly recommends the use of an atypically high pitch (he calls it a "supraoptimal" pitch level) for patients who "want immediate relief from their vocal symptoms." Raising the pitch level, Cooper claims, "takes the pressure off the laryngopharynx and very quickly alleviates or eliminates the vocal symptoms." In a contrary but more customary opinion, Russell[15] long ago stressed the association between vocal strain and the use of excessively high speaking or singing pitches.

The topic of suitable pitch generates more discussion than research. Conflicting conjectures dressed as dogmas abound. Clinically, a recommended change in pitch may produce fortuitous adjustments that bring relief from vocal fatigue. But there is no convincing logical or empirical reason for believing that all persons are naturally endowed with a single optimum speaking pitch, that it may be located by some uniform formula valid for all speakers and all speaking occasions, and that the range of hygienic pitches is necessarily narrow.

Stone and Sharf[16] have so far contributed the only direct experimental evidence relating pitch level to vocal fatigue. In their study, higher pitched phonations located at points 50% and 80% up each subject's total range produced earlier and greater voice change (heard fatigue) than did a lower pitched voice condition (similar to the modal conversational pitch of most persons) located at the 20% point. It remains to be investigated whether a still lower pitch is typically as detrimental to the voice (if not more so) than the use of a pitch that is too high.

FATIGUE AND LOUD VOICE

In the search for voice-damaging behaviors, none receives more mention than shouting or loud talking. Surprisingly, however, only a few studies have seriously documented the effects of loud voice use. Holbrook[17] reported the amount of time that 12 teachers spent talking, daily phonation time as well as daily loud (75 dB and above) phonation time. For five days each teacher wore a portable throat microphone connected to dual time meters. From this period of observation, Holbrook concluded that the amount of loud talking was related more to vocal fatigue than the amount of talking as such. One of two subjects who reported frequent vocal fatigue and occasional loss of voice was a physical education teacher. His daily average of loud phonation time was more than double the group average; his total phonation time, on the other hand, was not remarkable. The speech clinician talked the most of all the teachers but also showed the least amount of loud talking. No symptoms of vocal fatigue were reported by her.

Loud talking obviously affects persons differently. Case et al[18] observed ten basketball cheerleaders who presumably faced similar loud voice demands. Two of the cheerleaders developed vocal pathologies while the other eight escaped them. Whether the voice suffers from loud use is probably not entirely a matter of biological health or vigor. More than likely, vocal fatigue or its absence are also contingent on the precise behaviors employed in augmenting intensity: simultaneous changes in such dimensions as vocal attack and fundamental frequency, and the relative contributions (in effecting the loudness increase) of the respiratory and laryngeal musculature.

The point here is that increased intensity may seem to be responsible for vocal fatigue when changes such as marked pitch elevation and hard vocal attack have also occurred. Logically, vocal fatigue may be prevented if intensity is regulated more by respiratory than by laryngeal muscle forces. Some persons are understandably prone to fatigue if when they increase loudness they also exert needless laryngeal strain. But their voice problems in such instances result less from loud talking than from the unnecessary laryngeal hyperfunctions that may accompany it.

Support for such a position comes from the previously cited experiment by Stone and Sharf[16] who required ten normal men to phonate vowel lists at various pitches and intensities. Unlike their findings for pitch (earlier and greater voice changes for the higher than for the low-pitched voice condition), phonating more loudly did not result in an increase in judged (heard) vocal fatigue. Unfortunately, Stone and Sharf did not standardize the vowel samples from which judgments of voice change were made: loud voice samples were used for judging voice changes in the loud phonation condition, softer voice samples for the less loud conditions. The objection to such a procedure is that fatigue effects may become masked as intensity increases, like a cheerleader who fails to realize how badly she has "lost" her voice until she stops shouting.

But how then to explain the findings of Sander and Ripich[19] who confirmed a similar lack of relationship between loudness level and felt vocal fatigue? In this study, young men with normal voices were assigned loud (96 dB) or very loud (102 dB) talking. Each accrued ten minutes of phonation time (not speaking time) by repeating a sentence at loudness sufficient to simultaneously activate both a light and digital timer.

As a strategy for finishing in the shortest possible time, these subjects spoke a form of chant talk, prolonging the vowels that carry the primary speech power. Chant talk also involves a noticeable softening of vocal initiations, significant because "no way of singing or speaking" may be "more vocally fatiguing than using hard glottal attack."[20]

When reactions of voice change and discomfort resulting from loud and very loud speaking were assessed by questionnaire, less than half of Sander and Ripich's subjects (only 4 of 12 in the very loud condition) felt that their voices were less clear at the end compared with the beginning of the experiment. Talking more loudly did not hasten heard or felt fatigue. In fact, 11 of 12 subjects in the loud condition but only 6 of 12 in the very loud condition felt that speaking required more effort at the end compared with the beginning of the experiment.

If, as these results suggest, the hazards associated with loud talking are avoidable, then Cooper[14(p62)] is right to argue forcefully against settling for therapy goals that would make permanent voice cripples out of patients who lack the ability to produce loud voice easily and without strain. Brewer and Briess's[21] results from treating patients whose voice problems arose from constant loud speaking over industrial noise showed that successfully trained patients were reportedly able to resume their work and their talking in noisy environments without reappearance of voice symptoms.

EXPLANATIONS OF VOICE CHANGE

Although widely observed, the phenomenon of vocal fatigue is neither well understood nor well documented in physiologic or acoustic terms. Heard vocal fatigue is usually assumed to be myogenic. Of all the laryngeal muscles, the thyroarytenoid is apparently the most important for regulating phonatory style[22] and the most frequently implicated in voice breakdown.[23] Protracted strained phonation may cause these muscles to fatigue and the cords to become bowed during phonation.

In addition, misuse of the voice may create a fold lesion, but Harma et al[24] offer evidence that incautious vocal use during infection, not a faulty habitual phonatory style, is the most common cause of vocal nodules and polyps. An interesting question then is why patients with known lesions of the larynx seem so prone to vocal fatigue. It seems likely that habitual patterns of voice strain often emerge after disease onset. Bryce[25] believes that the laryngeal muscles fatigue from the additional effort expended to compensate for any small lesion that interferes with complete cord approximation.

Fatigue that is expressed muscularly may arise for neurogenic reasons. Haglund et al[26] offer electromyographic evidence that many patients who complain of abnormal vocal fatigue and whose voice problems are diagnosed as functional are instead suffering from an idiopathic paresis of the laryngeal muscles, not obvious enough to be observed by laryngoscopy. Vocal weakness with sustained effort may also be one of the first and only signs of myasthenia gravis.[27]

Speakers with usually normal voices commonly relate their episodes of vocal fatigue to periods of allergy or infection when the folds are presumably prone to inflammation. With aggravated use, the voice becomes weaker or breathier and may also become rough. Weakness or breathiness usually mean that glottic closure is short or incomplete; roughness usually means that the vibratory pattern of the folds is irregular. Are these changes due to a reflex influence on the muscles from the receptors of the altered mucous membrane?[28] Or is it because the laryngeal muscles tire under an added workload as cord edema increases? A simpler but not incompatible explanation is that the loss of mucosal mobility associated with increasing cord edema impairs the normal glottis closing action of the Bernoulli effect.[29] And when the edema is moderately severe or not uniformly distributed the periodicity of fold vibration is disturbed.[30]

The importance of fold microdynamics is suggested by the well-known fact that extended speaking often results in voice changes for the better. Sherman and Jensen[5] reported a decrease in scaled harshness for normal voices as a result of continuous oral reading; and 17 of 24 subjects in the Sander and Ripich[19] study reported voice improvement at some point during their loud speaking.

To explain this phenomenon of voice improvement with use — singers call it "warming up" — Sonninen et al[31] write that while unwanted edema is a common result of vocal misuse, a proper amount of tissue fluid is also apparently essential for achieving the best possible voice. The mobility of the cords is of course impaired with an excess of fluid, but if the cords are too dry and stiff the detrimental effect is similar.

VOICE ENDURANCE TESTING

The experimental study of vocal misuse by means of voice endurance testing remains largely unexploited. If vocal fatigue phenomena reflect improper voice use, they can also contribute to an overdue advance, from clinical conjecture to laboratory hypothesis testing, in knowledge of hygienic vocal behavior.

Relating how the voice is used to how quickly or how severely it fatigues when stressed may be approached from three design orientations. The first and most obvious approach is to identify the presumably detrimental behaviors that separate persons whose voices fatigue rapidly for no medical reason from those who, though in similar speaking or singing circumstances, seldom experience the problem. The approach can also be reversed: subjects with identifiably different vocal styles, defined physiologically and acoustically, can be tested for their fatigue proneness or resistance. And finally, of course, there is still much to be learned from asking subjects to phonate in prescribed ways and then determining how well these voices hold up. While each of these design approaches has its advantages, a better scientific understanding of optimum and abusive behavior is sure to emerge if they are pursued together.

Meanwhile, the need remains to help persons whose voices fatigue from misuse, especially those in voice-demanding occupations. Even before Jackson's[23] classic description of myasthenia laryngis, professionals have been warned to pay heed to the early signs of vocal fatigue that may presage a progressive difficulty. The typical tale is that of the singer who, after a period of vocal stress, finds himself unable to strike the note accurately, or to hold it after striking it. These or other voice symptoms may foretell future permanent impairment.[32]

But if the experience of audiologists is any guide, the scientific search for a simple formula relating short-term fatigue to future vocal handicap will prove disappointing. In the realm of hearing, at least, susceptibility to temporary noise-induced threshold shifts does not alone isolate those persons most at risk for permanent hearing loss. The time taken for recovery must be part of the equation.[33] And so it seems with the voice. Fleeting minor symptoms of fatigue occur even in well-trained singers, such as the part tone shifts detected in notes sung by members of the Vienna Boys Choir after a two-hour period of vocal stress.[34] Long recoveries are cause for concern. After only a brief period of loud voice use, Brewer and Briess's[21] patients with a history of laryngitis from speaking above industrial noise needed one hour for their voices to recover completely as compared with 10 to 30 seconds for controls and patients who had undergone successful voice therapy.

For patients whose voices tire rapidly but seem otherwise normal, the routine clinical use of voice endurance testing can highlight previously unobserved faults of voice production. There is hardly anything worthwhile to be learned from having such patients briefly read indifferent material in quiet unemotional voices. Those circumstances under which the voice tires must be duplicated or actually observed. Vocal fatigue phenomena offer the clinician the promise of a useful tool for assessing the desirability of alternate target voice goals in therapy. How well the voice endures is for many patients the most realistic way of evaluating therapy success.

REFERENCES

1. Moure E, Bouyer A. The abuse of the singing and speaking voice. London: Kegan Paul, Trench, Trubner, 1910.

2. Koike Y, von Leden H. Pathologic vocal initiation. Ann Otol Rhinol Laryngol 1969; 78:145.

3. Blakeley R. The practice of speech pathology. Springfield, Ill: Charles C. Thomas, 1972.

4. Brackett I. A study of the growth of inflammation of the vocal folds accompanying easy and harsh production of the voice. MA thesis, Northwestern University, 1940.

5. Sherman D, Jensen P. Harshness and oral reading time. J Speech Hear Dis 1962; 27:172-7.

6. Moore P. Organic voice disorders. Englewood Cliffs, NJ: Prentice-Hall, 1971:98.

7. Laguaite J, Waldrop W. Acoustic analysis of fundamental frequency of voices before and after therapy. Folia Phoniatr (Basel) 1964; 16:183-92.

8. Pronovost W. An experimental study of methods for determining natural and habitual pitch. Speech Monog 1942; 9: 111-23.

9. Harvey T, Howell P. Isotonic vocalis contraction as a means of producing rapid decreases in Fo. J Speech Hear Res 1980; 23:576-92.

10. Atkinson J. Correlation analysis of the physiological factors controlling fundamental voice frequency. J Acoust Soc Am 1978; 63:211-22.

11. Isshiki N. Regulating mechanism for voice intensity variation. J Speech Hear Res 1964; 7:17-29.

12. Coleman R, Mabis J, Hinson J. Fundamental frequency — sound pressure level profiles of adult male and female voices. J Speech Hear Res 1977; 20:197-204.

13. Perkins W. Vocal function: assessment and therapy. In: Travis L, ed. Handbook of speech pathology and audiology. New York: Appleton-Century-Crofts, 1971.

14. Cooper M. Modern techniques of vocal rehabilitation. Springfield, Ill: Charles C. Thomas, 1973.

15. Russell G. Etiology of follicular pharyngitis, catarrhal laryngitis, so-called clergyman's throat, and singer's nodes. J Speech Dis 1936; 1:113-22.

16. Stone R, Sharf D. Vocal change associated with the use of atypical pitch and intensity levels. Folia Phoniatr (Basel) 1973; 25:91-103.

17. Holbrook A. Instrumental analysis and control of vocal behavior. In: Cooper M, Cooper MH, eds. Approaches to vocal rehabilitation. Springfield, Ill: Charles C. Thomas, 1977.

18. Case J, Nenaber P, Beaver V. Laryngeal and vocal characteristics of university cheerleaders — a longitudinal study. Abstract. ASHA 1978; 20:774.

19. Sander E, Ripich D. Vocal consequences of loud talking. Abstract. ASHA 1981; 23:745.

20. Boone D. The voice and voice therapy. Englewood Cliffs, NJ: Prentice-Hall, 1977:131.

21. Brewer D, Briess F. Industrial noise: laryngeal considerations. NY State J Med 1960; 60:1737-40.

22. Hirano M, Koike Y, Joyner J. Style of phonation: an electromyographic investigation of some laryngeal muscles. Arch Otolaryngol 1969; 89:902-7.

23. Jackson C. Myasthenia laryngis. Arch Otolaryngol 1940; 32:434-63.

24. Harma R, Sonninen A, Vartiainen E, Haveri P, Vaisanen A. Vocal polyps and nodules. Folia Phoniatr (Basel) 1975; 27: 19-25.

25. Bryce D. Differential diagnosis and treatment of hoarseness. Springfield, Ill: Charles C. Thomas, 1974.

26. Haglund S, Knutsson E, Martensson A. An electromyographic study of the vocal and cricothyroid muscles in functional dysphonia. Acta Otolaryngol (Stockh) 1974; 77:140-9.

27. Aronson A. Early motor unit disease masquerading as psychogenic breathy dysphonia: a clinical case presentation. J Speech Hear Dis 1971; 36:115-24.

28. Dunker E, Schlosshauer B. Irregularities of the laryngeal vibratory pattern in healthy and hoarse persons. In: Brewer D, ed. Research potentials in voice physiology. Syracuse, NY: State University of New York Press, 1964.

29. Isshiki N. Recent advances in phonosurgery. Folia Phoniatr (Basel) 1980; 32:119-54.

30. Moore G. Observations on laryngeal disease, laryngeal behavior and voice. Ann Otol Rhinol Laryngol 1976; 85:553-64.

31. Sonninen A, Damste P, Jol J, Fikkens J, Roelofs J. Microdynamics in vocal vibration. Acta Otolaryngol (Stockh) 1974; 78:129-34.

32. Froeschels E, Jellinek A. Practice of voice and speech therapy. Boston: Expression Co, 1941:209.

33. Humes, L, Bess F. On the potential deterioration in hearing due to hearing aid usage. J Speech Hear Res 1981; 24:3-15.

34. Brunner W, Frank F. Der Einfluss einer mehrstundingen stimmlichen Belastung auf die Stingstimme der wiener Sangerknaben. Folia Phoniatr (Basel) 1978; 30:22-7.

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WEST VIRGINIA ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY

The annual spring meeting of the West Virginia Academy of Otolaryngology-Head and Neck Surgery will be held May 28-30, 1983, at The Greenbrier. For further information contact James L. Bryant, MD, Secretary Treasurer, 125 North Sixth Street, Clarksburg, WV 26301; (304) 623-6533.

Ann Otol Rhinol Laryngol 92:1983

NYSTAGMUS OF PAROXYSMAL POSITIONAL VERTIGO

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During attacks of paroxysmal positional vertigo in 12 patients, nystagmus in different gaze positions was observed visually and recorded by electronystagmography (eyes open, fixating). Visually observed eye movement was similar in all cases, with oblique (upward and horizontal) and rotatory (clockwise during leftward movement) components in the fast phase; rotation dominated on ipsilateral gaze (toward the lower ear) and oblique movement dominated on contralateral gaze. However, ENG recordings showed greater variability and were often inconsistent with visual observation; the horizontal component often reversed with change in gaze position, and dissociated eye movements, as well as down-beating nystagmus, were sometimes seen. More sophisticated measurement and strict attention to gaze position is required to resolve these discrepancies.

INTRODUCTION

Paroxysmal positional vertigo is a syndrome characterized by recurring, sudden, brief attacks of vertigo, which are provoked by changes in head position. Attacks are most frequently reported on turning from side to side in bed, or on lying down or rising from bed, but they also occur on bending forward, or on turning the head up while standing or sitting. They do not last more than some seconds, but are frequently violent and alarming. On clinical examination, the paroxysm of vertigo characteristically follows the change in head position after a latent period of some seconds, and repeated positioning results in progressive reduction ("fatigue") in the intensity of the paroxysm.

Adler[1] described cases of paroxysmal positional vertigo in 1897, but it was Barany[2] who, in 1921, first gave a detailed description of the attack and tried to explain the pathophysiologic mechanism. Borries[3] appears to have been the first (1925) to describe a positioning maneuver to elicit an attack. Dix and Hallpike[4] in 1952 reported a large series of cases, called the condition "positional nystagmus of the benign paroxysmal type," and described the well-known "Hallpike maneuver" for positioning the patient so as to elicit an attack. Stenger[5] described a number of cases in which the attack occurred when the patient was moved quickly from the sitting to the head-hanging position without the concomitant head turning which is part of the Hallpike maneuver. Stahle and Terrins[6] studied a series of 80 cases, using both clinical and electronystagmographic (ENG) examination, and suggested a classification scheme based on the type of positioning maneuver which elicited an attack and on the direction of the nystagmus. A study of clinical and routine ENG findings in 255 cases seen by one of us (AK) has recently been reported.[7]

The nystagmus observed during the paroxysmal attack has a prominent rotatory component, combined with a linear component which is oblique or vertical. The sense of the rotatory component is rarely described explicitly, but in our experience it appears to be clockwise when the horizontal component is to the left. In studies based on visual observation, it is reported that the horizontal component is usually toward the lowermost ear following Hallpike positioning, while the vertical component is upward (frontal).[4,5] Barany[2] noted that the relative prominence of rotatory and linear components of the nystagmus varies with the direction of gaze; rotation is prominent when the eyes are deviated toward the lower ear in the provocative head position, whereas the nystagmus becomes almost purely oblique or vertical during gaze in the opposite direction.

ENG recordings of horizontal and vertical components of the nystagmus have been made by several investigators,[6-10] and the findings are not entirely consistent with visual observations. The vertical component of the fast phase is almost invariably upward (frontal), and is usually pronounced. The horizontal component is more variable, in magnitude as well as direction. Stahle and Terrins[6] found that in most cases the horizontal component beat toward the lowermost ear in the provocative head position, but this conclusion appears to have been based on pooled data based on visual observation as well as ENG recordings. Baloh et al[9] report that in 23 patients whose attacks occurred only in one head-hanging position, the horizontal component of the recorded nystagmus was always away from the lower ear; in nine patients who had attacks in both head-hanging positions, the nystagmus was more prominent in one position and its direction was the same in both. They also found that monocular ENG

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TABLE 1. SUMMARY OF ROUTINE ENG FINDINGS

	Positional Nystagmus (eyes closed)			*Bithermal Caloric Responses*			
					Preponderance		*No. of*
Diagnosis	*None*	*DC*	*DF*	*Sym.*	*Labyr.*	*Direct.*	*Cases*
Head injury			3		2	1	3
Menière's disease			1		1		1
Vestibular neuronitis		1			1		1
Idiopathic	2	3	2	5		2	7

DC - Direction changing; DF - Direction fixed; Sym. - Symmetrical; Labyr. - Labyrinthine; Direct. - Directional.

recordings always showed dissociated eye movement. The vertical component was greater in the lowermost eye and the horizontal component was usually toward the lower ear in the upper eye and away from the lower ear in the lower eye. It may be significant that the recordings of Baloh et al were made with eyes closed, whereas most other reported recordings of paroxysmal nystagmus have been made with eyes open.

It appears from these ENG studies that nystagmus beating away from the lower ear in the provocative head position is more commonly seen in ENG recordings than on visual observation. Moreover, Barber and Stockwell[8] and Katsarkas and Kirkham[7] have reported cases in which the direction of the horizontal component recorded by ENG was opposite to that observed visually.

Karsarkas and Kirkham[7] also observed that in one case the direction of the horizontal component of nystagmus reversed abruptly during a paroxysmal attack, and speculated that this might be related to a sudden change in the position of gaze. As already noted, it has been known since the report of Barany that the nystagmus is affected by the direction of gaze, but it does not appear to have been suggested previously that the direction of nystagmus might actually be reversed by a change in gaze direction.

The present study was undertaken in order to test this hypothesis, and also to investigate discrepancies between visual observation and ENG recordings.

CASES AND METHODS

Twelve patients, ranging in age from 43 to 64 years, and examined by one of us (AK), were selected for the study because they gave a history typical of paroxysmal positional vertigo, their vertigo and the characteristic nystagmus were reproduced by the Hallpike maneuver during the initial examination, and it seemed likely that they would be able to follow instructions during the brief but highly distressing period of the paroxysm. In five patients the syndrome appeared subsequent to possibly related disorders, while in seven no relevant antecedent disorder was identified (Table 1); the latter cases were classified as idiopathic.

On clinical examination, no abnormalities were found except 1) a degree of hearing loss in some patients (see below); 2) a degree of unsteadiness in some patients; 3) in three patients, gaze nystagmus toward the ear which was lowermost in the provocative head position; and 4) paroxysmal positional vertigo, which in all cases could be elicited by the Hallpike maneuver but not by the Stenger; attacks occurred in one head-hanging position only, except in one post-head-injury patient, who had attacks in both right and left head-hanging-positions. The audiogram in 11 cases showed no hearing loss, or some symmetrical, bilateral, sensorineural loss. The patient with Menière's disease showed substantial sensorineural loss in one ear; hearing in the other ear was close to normal. Routine ENG examination (gaze and positional nystagmus, caloric test), performed in all patients, gave the results shown in Table 1. No gaze nystagmus was recorded.

The actual attack was recorded prior to the routine caloric examination, according to the following procedure. Each patient was tested for gaze and positional nystagmus in the caloric test position, given detailed instructions as to what he or she would be required to do during the attack, and then brought very slowly to the sitting position with head straight. After recording for 30 seconds in this position, the patient was moved quickly, using the Hallpike maneuver, to the provocative head-hanging position with eyes open. The patient was immediately asked to fixate on the examiner's finger in a horizontal gaze deviation of approximately 30° in one direction or the other. After a few seconds, when the paroxysm of nystagmus was well developed, the patient was asked to turn his or her eyes quickly, following the examiner's finger, to a gaze deviation of about 30° in the other direction. Eye movement recording was then continued until the nystagmus subsided. During this rather brief period of time, the examiner observed the nystagmus, while the technician attended to details of the chart recording.

Eye movements were recorded using Beckman miniature Ag-AgCl skin electrodes. In eight cases, horizontal eye movement was recorded using bitemporal leads and vertical movement was recorded from the right eye. Separate, horizontal eye leads were used in four patients. Recordings were made on a standard chart recorder after AC amplification with a time constant of three seconds and a bandwidth of 30 Hz.

RESULTS

VISUAL OBSERVATIONS

In all patients, the nystagmus was mainly rotatory when the eyes were deviated toward the lower ear, and mainly oblique when they were deviated toward the upper ear. The nystagmus observed visually was complex, especially when the eyes were deviated toward the lower ear, when it appeared that each quick phase of nystagmus involved a rotation of the eye about the visual axis, combined with motion in a more or less semicircular arc in an upwardly oblique direction. In the patient's frame of reference, rotation was clockwise (the superior pole of the eye moved left) when the "horizontal" component of the quick phase of nystagmus was to the patient's left. On gaze toward the upper ear, the degree of rotation during each quick phase was less, and eye movement appeared to be predominantly oblique. The direction of this oblique component varied from patient to patient, ranging from almost "upward" (frontal) to almost "horizontal" toward the lower ear; it never appeared to be "downward" or toward the upper ear.

Note that during the period of observation the examiner was preoccupied with a) monitoring gaze position, and b) assessing changes in the nystagmus pattern associated with changes in gaze position. He was not concerned at the time with the possibility that eye movement in the two eyes might differ sub-

TABLE 2. SUMMARY OF ENG FINDINGS DURING PAROXYSMAL VERTIGO

Bitemporal and Vertical Recordings

Case No.	*Head Position*	*Ipsi. Gaze Hor.*	*Ipsi. Gaze Vert.*	*Cont. Gaze Hor.*	*Cont. Gaze Vert.*
4	R	Ipsi.	—	Cont.	Up
5	L	Ipsi.	Down	Cont.	—
6	R	—	—	Cont.	Up
7	L	Cont.	—	Cont.	—
8	L	—	Up	Cont.	—
9	L	Cont.	Down	Cont.	—
10	L	Ipsi.	Up	Ipsi.	Up
	R	Ipsi.	Down	Cont.	Up

Single-eye Horizontal Recordings

Case No.	*Head Position*	*Ipsi. Gaze Ipsi. Eye*	*Ipsi. Gaze Cont. Eye*	*Central Gaze Ipsi. Eye*	*Central Gaze Cont. Eye*	*Cont. Gaze Ipsi. Eye*	*Cont. Gaze Cont. Eye*
1	L	Cont.	Cont.	Cont.	Cont.		
2	R	—	Ipsi.	—	—	Cont.	Cont.
3	L	Cont.	Ipsi.	—	—	Cont.	Cont.

Ipsi. - Ipsilateral; Cont. - Contralateral; Hor. - Horizontal; Vert. - Vertical.

stantially, and, in retrospect, was unable to make a firm statement on this point.

ENG RECORDINGS

Satisfactory tracings from both bitemporal and vertical leads were obtained in seven cases, and from separate horizontal leads in three cases. Nine patients whose attacks were successfully recorded showed nystagmus in one head-hanging position only; in one patient nystagmus was recorded in both head-hanging positions. The horizontal slow-phase velocity of nystagmus at the peak of the attack ranged from 25 to 135°/s. The results are summarized in Table 2.

Bitemporal Horizontal Leads (7 Cases). In two cases the fast phase of nystagmus was ipsilateral (toward the lower ear) during gaze in this direction, and reversed during contralateral gaze. In two cases the fast phase was contralateral in both directions of gaze. In two cases nystagmus was recorded only during contralateral gaze, with fast phase contralateral. In the bilateral case, in whom an attack was provoked in both head-hanging positions, fast phase was ipsilateral during ipsilateral gaze; it reversed during contralateral gaze in the right head-down position but remained unchanged in the left head-down position.

Vertical Leads. In the bilateral case, the nystagmus was down-beating in the right (Fig 1A) and up-beating in the left head-down position (Fig 1B) on ipsilateral gaze; on contralateral gaze the nystagmus was up-beating in both head positions. In one case no vertical nystagmus was recorded, and in the remaining five cases it was recorded only in one gaze position; during ipsilateral gaze it was down-beating in two cases and up-beating in one case, while during contralateral gaze it was up-beating in two cases.

Separate Horizontal Lead (3 Cases). Case 1) On ipsilateral gaze, both eyes beat toward the contralateral ear, but slow-phase velocity was greater in the ipsilateral eye; on central gaze, nystagmus direction was unchanged and slow-phase velocity was approximately the same in both eyes (Fig 2). Case 2) On ipsilateral gaze, the contralateral eye beat ipsilaterally, while nystagmus in the ipsilateral eye was not satisfactorily recorded; on contralateral gaze, both eyes beat toward the contralateral ear (Fig 3). Case 3) On ipsilateral gaze, the ipsilateral eye beat contralaterally and the contralateral eye beat ipsilaterally; on contralateral gaze, both eyes beat contralaterally (Fig 4).

DISCUSSION

On visual observation, the fast phase of nystagmus in the patients who participated in this study always appeared to have a linear component beating in an upwardly oblique direction toward the lower ear, and a rotational component beating clockwise when the "horizontal" component was to

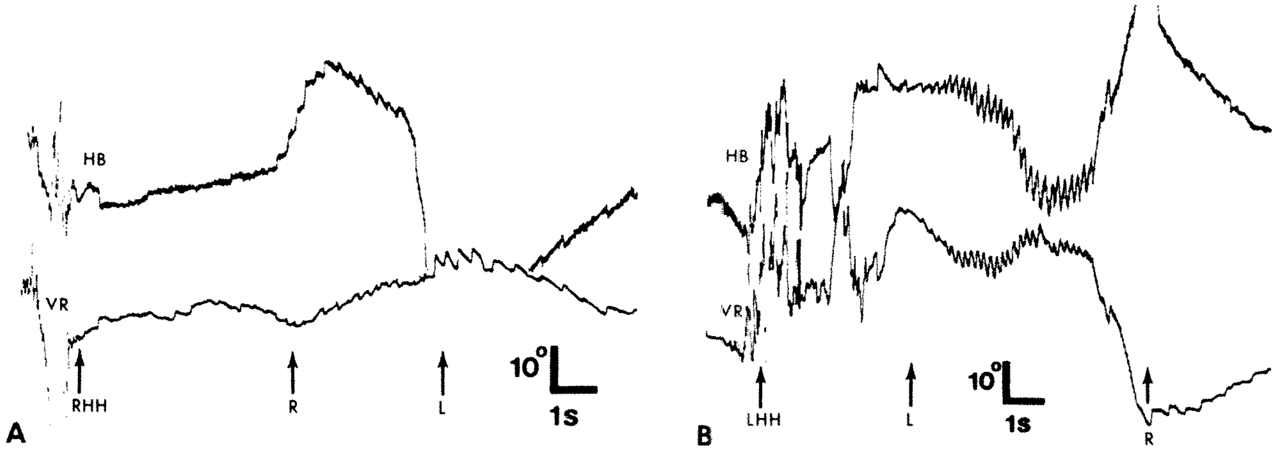

Fig 1. (Case 10) Recording during a paroxysm, post-head injury. A) Right head-hanging position. RHH - Right head-hanging position assumed; R - Right (ipsilateral) gaze; L - Left (contralateral) gaze. B) Left head-hanging position. LHH - Left head-hanging position assumed; R - Right (contralateral) gaze; L - Left (ipsilateral) gaze. HB - Bitemporal horizontal recording; VR - Vertical recording, right eye. In all figures, rightward and upward eye deviation is recorded upward.

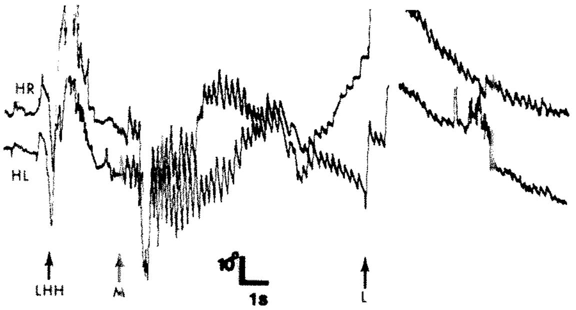

Fig 2. (Case 1, idiopathic) Recording during a paroxysm in the left head-hanging position. Slow-phase eye velocity reached 135°/s in this case. HL - Horizontal left eye recording; HR - Horizontal right eye recording; M - Beginning of the attack, eyes in midposition; L - Left (ipsilateral) gaze.

the left, and anticlockwise when the "horizontal" component was to the right. (In other patients we have, infrequently, seen nystagmus beating away from the lower ear.) The rotational component was more prominent on gaze toward the lower ear, and the vertical component more prominent on gaze toward the upper ear. Dissociated eye movements were not noted on visual observation.

ENG recordings in the same patient gave quite a different picture. With bitemporal leads, on ipsilateral gaze (toward the lower ear) the fast phase of nystagmus beat ipsilaterally in 4 of 6 attacks in which a satisfactory recording was obtained in this gaze position, and beat contralaterally in two; on contralateral gaze, nystagmus beat ipsilaterally in one attack and contralaterally in seven. With separate horizontal leads, results (in only three cases) were less clear; on central gaze (one case) and contralateral gaze (two cases) both eyes beat contralaterally; on ipsilateral gaze, in one case both eyes beat contralaterally, in one case the ipsilateral eye beat contralaterally and the contralateral eye beat ipsilaterally, and in the third case the contralateral eye beat ipsilaterally and the nystagmus was not recorded in the other eye. The vertical component of nystagmus on contralateral gaze was up-beating in four attacks and not recorded in four; on ipsilateral gaze, nystagmus was up-beating in two attacks, down-beating in three, and not recorded in three.

These findings confirm previous reports that the nystagmus of paroxysmal positional vertigo varies with gaze direction, and show clearly that a change in the direction of gaze can result in *reversal* of the direction of nystagmus during the attack. Dissociation of movement in the two eyes was confirmed, but was not striking; horizontal eye movement in opposite directions in the two eyes was recorded in one case, and a marked difference in slow-phase velocity in the two eyes was seen in another.

An important result of this study is the finding that the direction of nystagmus in ENG recordings is frequently different from that reported on visual observation in the same patient. It must be acknowledged that visual detection of the direction of nystagmus is difficult to judge under the conditions of the Hallpike test, and the difficulty was even greater in this study, since the examiner was also monitoring gaze position. Nevertheless, there appears to be a real discrepancy in some cases, and one must ask whether the human observer or the ENG recording is in error. The presence of a significant rotational component of eye movement, particularly on gaze toward the lower ear, when discrepancies were most marked, might well result in human perceptual error. On the other hand, the reliability of horizontal and vertical components of the ENG in the presence of gaze deviation and eye rotation is not well known, and must also be suspect.

Resolution of this discrepancy requires more sophisticated recording techniques, and may be important clinically, since the direction of eye movement during the attack has been used as one criterion for classifying patients with paroxysmal positional vertigo.[6] The question is also interesting in connection with the hypothesis that attacks result from transient stimulation of the posterior semicir-

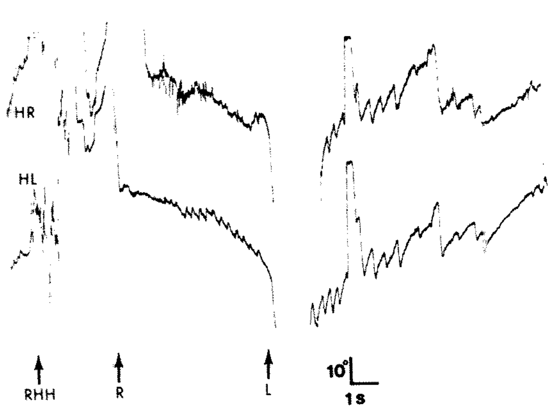

Fig 3. (Case 2, idiopathic) Recording during a paroxysm in the right head-hanging position. L - Left (contralateral) gaze; R - Right (ipsilateral) gaze.

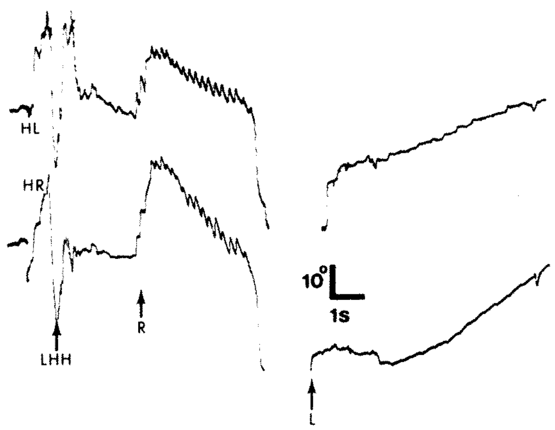

Fig 4. (Case 3, idiopathic) Recording during a paroxysm in the left head-hanging position. L - Left (ipsilateral) gaze; R - Right (contralateral) gaze.

cular canal;[11-13] gaze position is known to affect the nystagmus produced experimentally by posterior canal stimulation.[14]

An immediate conclusion is that it is imperative that gaze position be carefully controlled in any study of the nystagmus of paroxysmal positional vertigo, and probably of other conditions in which the nystagmus has a prominent rotatory component.

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REFERENCES

1. Adler. Ueber den 'einseitigen Drehschwindel.' Dtsch Z Nervenheilkd 1897; 11:358-75.
2. Barany R. Diagnose von Krankheitserscheinungen im Bereiche des Otolithenapparates. Acta Otolaryngol (Stockh) 1921; 2:434-7.
3. Borries G. Statisch (Zephalostatisch) ausgelöster Nystagmus. Arch Ohren Nasen Kehlkopfheilkd 1925; 112:53-63.
4. Dix MR, Hallpike CS. The pathology, symptomatology and diagnosis of certain common disorders of the vestibular system. Proc R Soc Med 1952; 45:341-54.
5. Stenger HH. Ueber Lagerungsnystagmus unter besonderer Berücksichtigung des gegenlaufigen transitorischen Provokationsnystagmus bei Lagewechsel in der Sagittalebene. Arch Ohren Nasen Kehlkopfheilkd 1955; 168:220-68.
6. Stahle J, Terrins J. Paroxysmal positional nystagmus. Ann Otol Rhinol Laryngol 1965; 74:69-83.
7. Katsarkas A, Kirkham T. Paroxysmal positional vertigo — a study of 255 cases. J Otolaryngol 1978; 7:320-30.
8. Barber HO, Stockwell CW. Manual of electronystagmography. St. Louis: CV Mosby 1976; 136-40.
9. Baloh RW, Sakala SM, Honrubia V. Benign paroxysmal positional vertigo. Am J Otolaryngol 1979; 1:1-6.
10. Coates AC. Electronystagmography. In: Bradford LJ, ed. Physiological measures of the audio-vestibular system. New York: Academic Press, 1975.
11. Schuknecht HF. Pathology of the ear. Cambridge, Mass: Harvard University Press, 1974:465-73.
12. Gacek RR. Further observations on posterior ampullary nerve transection for positional vertigo. Ann Otol Rhinol Laryngol 1978; 87:300-5.
13. Harbert F. Benign paroxysmal positional nystagmus. Arch Ophthalmol 1970; 84:298-302.
14. Cohen B, Suzuki J, Bender M. Nystagmus induced by electrical stimulation of ampullary nerves. Acta Otolaryngol (Stockh) 1965; 60:422-36.

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FOURTH WORLD CONGRESS ON BRONCHOESOPHAGOLOGY

The Fourth World Congress on Bronchoesophagology will take place at the Foresta Conference Center in Stockholm, Sweden, June 20-23, 1983. This Congress is arranged by the International Bronchoesophagological Society, Swedish Otolaryngological Society and Swedish Society for Pulmonary Diseases. During the meeting, the Congress will update the knowledge within bronchology and esophagology. Further information may be obtained by writing IBES Congress 1983, c/o RESO Congress Service S-105, 24 Stockholm, Sweden, or Dr. Stig Haglund, Secretary of the Congress, Dept. of Otolaryngology, Karolinska Sjukuset, S-104 01 Stockholm 60, Sweden.

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AUTONOMIC INNERVATION OF THE MIDDLE EAR

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The distribution of nerve fibers in the middle ear mucosa and eardrum of the cat and guinea pig was studied using immunocytochemical and histofluorescence techniques. Nerve fibers containing noradrenaline, vasoactive intestinal peptide, substance P, enkephalin or immunoreactive avian pancreatic polypeptide were demonstrated in the middle ear mucosa. After extirpation of the superior cervical ganglion, nerve fibers containing noradrenaline and avian pancreatic polypeptide disappeared while fibers containing vasoactive intestinal peptide, substance P and enkephalin seemed to remain unaffected.

The upper respiratory tract is richly supplied with peptide-containing nerve fibers. Thus, recent immunocytochemical studies have revealed fibers containing vasoactive intestinal peptide (VIP), substance P (SP) or immunoreactive avian pancreatic polypeptide (APP).[1-3] The distribution of these fibers in the nasal mucosa has been rather extensively studied while the autonomic innervation of the middle ear has received less attention. In a study of the middle ear mucosa of the cat Ishii and Kaga[4] observed numerous acetylcholinesterase-positive nerve fibers. In addition, using electron microscopy they demonstrated nerve fibers containing small dense cored vesicles of the type seen in adrenergic fibers.[4] In the present study we have analyzed the middle ear and the eardrum of guinea pigs and cats using the Falck-Hillarp histofluorescence method for the demonstration of adrenergic fibers as well as immunocytochemical methods for the demonstration of peptide-containing nerve fibers.

MATERIAL AND METHODS

Twenty guinea pigs and nine cats of either sex were used. They were sacrificed by exsanguination under diethyl ether anesthesia (guinea pigs) or pentobarbitone anesthesia (cats). In addition, the left superior cervical ganglion was removed from five guinea pigs under ketalar anesthesia. These animals were killed 6-9 weeks later. Specimens from the middle ear mucosa and eardrum were dissected out and processed for histochemistry as follows.

Demonstration of Adrenergic Nerve Fibers. Specimens from the middle ear mucosa of four cats and four guinea pigs were stretched on clean microscope slides, dehydrated in a desiccator over phosphorus pentoxide and exposed to formaldehyde gas at 80°C for one hour.[5] In addition, specimens from the middle ear mucosa of three guinea pigs were immersed for 30 minutes in a freshly-made solution of glyoxylic acid in phosphate buffer.[6] They were then stretched on microscope slides and dried three hours under a hairdrier (70°C). All specimens were mounted in Entellan (Merck Darmstadt, FRG) and examined with a fluorescence microscope.[5,6]

CHARACTERISTICS OF PEPTIDE ANTISERA USED

Antisera Raised Against	*Code*	*Working Dilution*	*Source*
VIP	7852	1:320	R. Ekman, Malmö General Hosp., Malmö, Sweden
Substance P	SP-8	1:80	P. Emson, Cambridge Univ., Cambridge, UK
Leu-enkephalin	170	1:60	K-J. Chang, Burroughs Wellcome, Research Triangle Park, NC
Avian pancreatic polypeptide	—	1:80	J.R. Kimmel, Univ. of Kansas, Kansas City

Demonstration of Peptidergic Nerve Fibers. Specimens from the middle ear mucosa of 13 guinea pigs and five cats were stretched on microscope slides as whole mounts, fixed in a mixture of formaldehyde and picric acid, dehydrated, cleared in xylene and hydrated.[7] The whole mount preparations were then processed for the immunocytochemical demonstration of VIP, SP, enkephalin and APP. Details on the antisera are given in the Table.

The VIP antiserum does not cross-react with other neuropeptides (enkephalin, substance P, somatostatin, neurotensin, gastrin/CCK tested) nor with chemically related peptides such as secretin, glucagon or gastric inhibitory peptide.[8]

The SP antiserum does not cross-react with bombesin which shares the COOH-terminal two amino acids with SP. It does, however, cross-react with physalaemin[9] which shares five amino acid residues with SP and recently is claimed to occur in nerve fibers in the mammalian gastrointestinal tract.[10]

In both immunochemical and immunocytochemical tests the leu-enkephalin antiserum has been found to cross-react to some extent with met-enkephalin but not at all with the endorphins or β-lipotropin.[11]

The APP antiserum has been used in several immunocytochemical studies.[3,7,12,13] Neuronal APP is not demonstrated using antibodies against mammalian pancreatic polypeptide (PP). Therefore, neuronal APP is probably distinct from hormonal PP.[12]

Cross reactivity with unknown peptides containing immunoreactive amino acid sequences recognized by the different antisera cannot be excluded. Therefore, it would be appropriate to name the immunoreactive material VIP-like, SP-like, enkephalin-like, and APP-like. For brevity, the immunoreactive nerve fibers are referred to as VIP, SP, enkephalin and APP nerve fibers in the text

For immunofluorescence, the site of the antigen-antibody reaction was revealed by fluorescein isothiocyanate-labelled goat

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From the Department of Otolaryngology, University Hospital, Malmö, Sweden, Kansai Medical University, Moriguchi, Osaka, Japan, and the Department of Histology, University of Lund, Sweden. This project was supported by a grant from the Swedish MRC (project no. 14x-4499).

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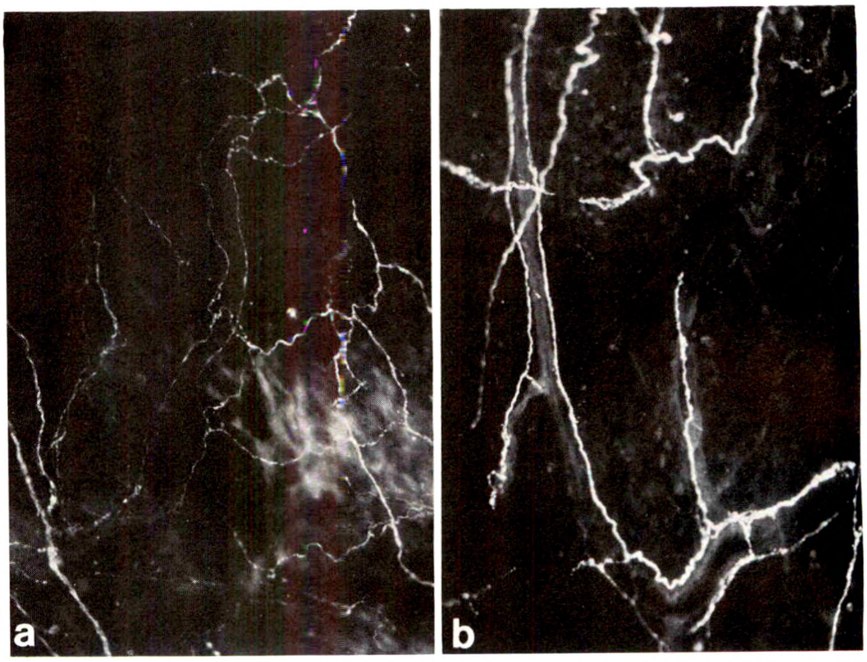

Fig. 1. Guinea pig middle ear mucosa. Fluorescence histochemical demonstration of adrenergic nerve fibers. Numerous nerve fibers are seen a) in mucosal stroma and b) around blood vessels. (a, x 141; b, x 221)

anti-rabbit IgG (provided by SBL, Stockholm) diluted 1:20. Specimens incubated with antiserum inactivated by the addition of excess antigen (10-100 μg of synthetic SP and synthetic enkephalin [both provided by Beckman SA, Geneva], pure porcine VIP and pure avian PP respectively) were used as controls.

RESULTS

Numerous fine varicose adrenergic nerve fibers were seen in the middle ear mucosa of both cats and guinea pigs (Fig. 1a). Most of the fibers were associated with small blood vessels (Fig. 1b). In addition, certain fibers were seen to run in the mucosa without obvious relation to blood vessels. Also fibers containing VIP (Fig. 2), SP (Fig. 3), enkephalin (Fig. 4a) or APP (Fig. 4b) were observed in both species examined. Most of the VIP, SP and APP fibers were associated with small blood vessels, but single fibers occurred also in the mucosal stroma without obvious relation to blood vessels. A few enkephalin fibers were observed in the mucosa without relation to blood vessels. After extirpation of the left cervical superior ganglion the adrenergic and APP-containing fibers in the ipsilateral middle ear mucosa disappeared while VIP and SP fibers were unaffected. Due to the scarce number of enkephalin-containing fibers it was not possible to assess the effect of ganglionectomy on this type of nerve fiber.

In the eardrum an occasional nerve fiber containing SP was seen without obvious relation to blood vessels. Nerve fibers containing noradrenaline, VIP, enkephalin or APP could not be demonstrated.

DISCUSSION

In the present study adrenergic nerve fibers as well as fibers storing VIP, SP, enkephalin or APP

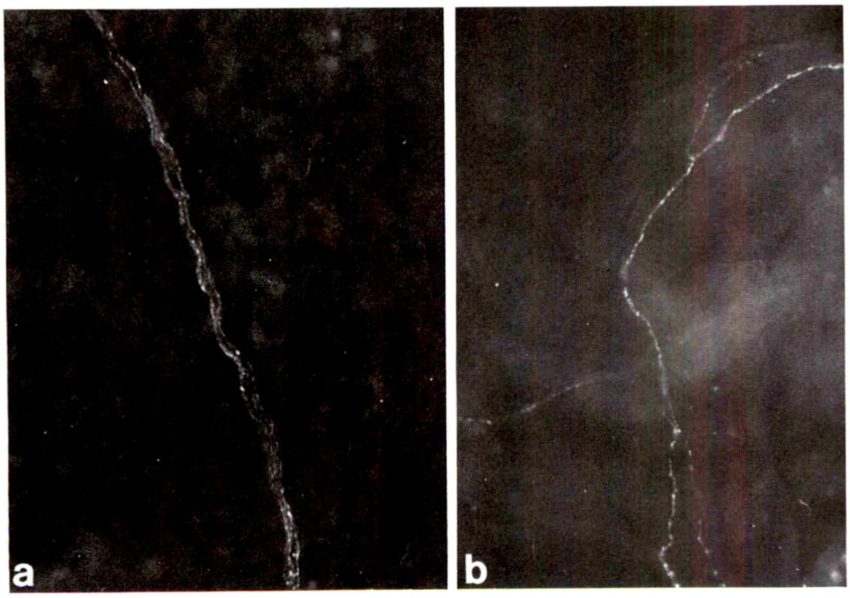

Fig. 2. Immunocytochemical demonstration of VIP. a) Cat middle ear mucosa. Nerve bundle containing several VIP immunoreactive fibers. b) Guinea pig middle ear mucosa. Single thin VIP immunoreactive nerve fiber. (x 211)

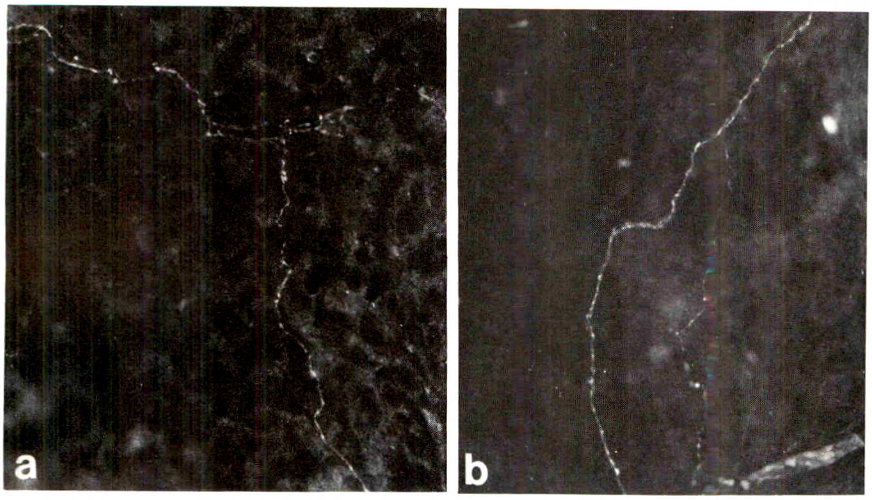

Fig. 3. Immunocytochemical demonstration of substance P in a) fine varicose nerve fibers in middle ear mucosa of cat and in b) thin varicose fibers in middle ear mucosa of guinea pig. (x 227)

were seen in the middle ear mucosa of cats and guinea pigs. Most of the fibers were associated with blood vessels but fibers without relation to blood vessels were also seen. The adrenergic and APP-containing nerve fibers disappeared after extirpation of the superior cervical ganglion. With respect to the adrenergic fibers the present results confirm those obtained by Ishii and Kaga.[4] These authors demonstrated nerve fibers containing small dense cored vesicles after treatment with 5-hydroxydopamine, an agent known to accumulate selectively in adrenergic fibers. Due to their intimate relation with blood vessels the bulk of the nerve fibers demonstrated in the present study may be implicated in vasomotor functions. The actions of catecholamines on blood vessels have been the subject of many recent reviews.[14] Immunocytochemical studies have demonstrated a rich supply of VIP, SP, and APP fibers around both cerebral[7,5,16] and peripheral blood vessels.[12,17,18] VIP and SP seem to have dilatory actions.[16,17,19,20] The vasomotor actions of APP are not known.

There is evidence that certain peripheral SP fibers may be involved in sensory transmission.[18,21] Therefore, at least a proportion of the SP fibers may represent peripheral ramifications of sensory neurons.

Enkephalin-containing nerve fibers have previously been found in the central nervous system[22] including the inner ear[23] as well as in several peripheral organs such as the gut.[11] Their functional role in the middle ear mucosa is enigmatic.

Pancreatic polypeptide is a peptide produced by endocrine cells in the pancreas and gut.[24] Certain antisera raised against avian PP and antisera raised against the synthetic C-terminal hexapeptide of mammalian PP[25] demonstrate not only endocrine cells but also neuronal elements in the brain and periphery. Still we do not know if the neurons demonstrated by the two types of PP antisera are identical. Recent observations have shown that sympathetic ganglia are rich in APP-immunoreactive nerve cell bodies.[13] Available evidence suggests that the neurons storing immunoreactive APP are identical with a population of adrenergic neurons.[7,13] The

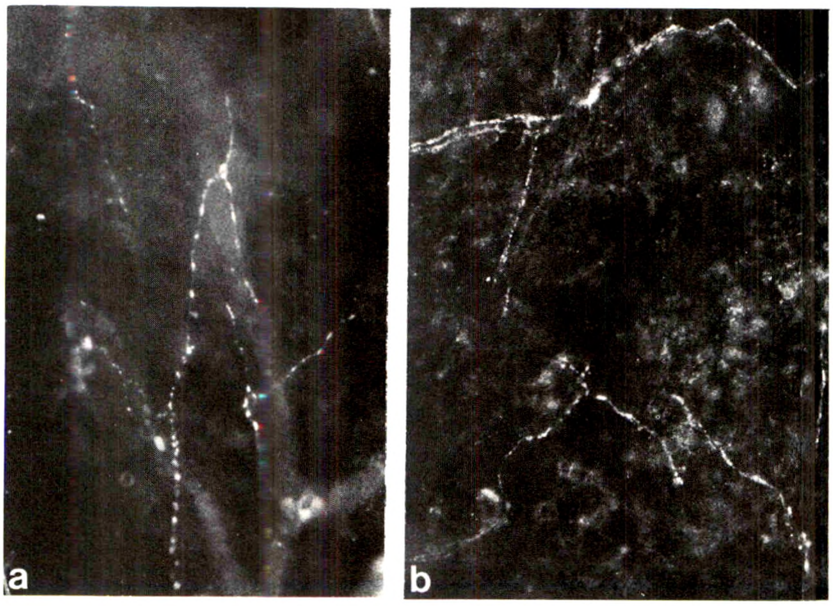

Fig. 4. Guinea pig middle ear mucosa showing fine varicose fibers containing a) immunoreactive avian pancreative polypeptide (x 250), and b) immunoreactive enkephalin (x 218).

present results indicating that APP immunoreactive fibers in the middle ear originate in the superior cervical ganglion support this view.

The eardrum has a well-developed supply of small blood vessels. Studies using methylene blue staining[26] have indicated that the eardrum in addition is rich in nerve fibers and that the blood vessels in particular are supplied with numerous nerve fibers. Somewhat surprisingly therefore the present study revealed only a very sparse supply of SP fibers in the eardrum but no other peptide-containing or adrenergic fibers.

In conclusion, the present study has shown that the middle ear mucosa is supplied with autonomic nerve fibers, peptide-containing as well as adrenergic. It is conceivable that they serve as local regulators of vasomotor and possibly also secretory functions.

ACKNOWLEDGMENTS — The authors wish to thank Dr. V. Mutt, Stockholm, for his gift of pure porcine VIP, and Dr. J. R. Kimmel for his gift of pure avian PP.

REFERENCES

1. Uddman R, Alumets J, Densert O, Håkanson R, Sundler F. Occurrence and distribution of VIP nerves in the nasal mucosa and tracheobronchial wall. Acta Otolaryngol (Stockh) 1978; 86: 443-8.

2. Uddman R, Malm L, Sundler F: Peptide containing nerves in the nasal mucosa. Rhinology 1981; 19:75-9.

3. Uddman R, Håkanson R, Sundler F. Immunoreactive avian pancreative polypeptide occurs in nerves of the mammalian nasal mucosa and eustachian tube. ORL 1980; 42:242-8.

4. Ishii T, Kaga K. Autonomic nervous system of the cat middle ear mucosa. Ann Otol Rhinol Laryngol 1976; 85 Suppl 25: 51-7.

5. Björklund A, Falck B, Owman C. Fluorescence microscopic and microspectrofluorometric techniques for the cellular localization and characterization of biogenic amines. In: Berson SA, ed. Methods of investigative and diagnostic endocrinology. Vol 1. Amsterdam: North-Holland Pub Co, 1972:318-68.

6. Lindvall O, Björklund A. The glyoxylic acid fluorescence histochemical method: a detailed account of the methodology for the visualization of central catecholamine neurons. Histochemistry 1974; 39:97-127.

7. Uddman R, Edvinsson L, Håkanson R, Owman C, Sundler F. Immunohistochemical demonstration of APP (avian pancreatic polypeptide)-containing nerve fibres in cerebral blood vessels. Brain Res Bull 1982; 9:715-8.

8. Sporrong B, Falkmer S, Robboy SJ, et al. Neurohormonal peptides in ovarian carcinoids. An immunohistochemical study of eighty-one primary carcinoids and of intra-ovarian metastases from six mid-gut carcinoids. Cancer 1982; 49:68-74.

9. Brodin E, Alumets J, Håkanson R, Leander S, Sundler F. Immunoreactive substance P in chicken gut, distribution, ontogeny and possible functional significance. Cell Tissue Res 1981; 216:455-69.

10. Lazarus LH, Linnoila RI, Hernandez O, Di Augustine RP. A neuropeptide in mammalian tissue with physalaemin-like immunoreactivity. Nature 1980; 287:555-8.

11. Alumets J, Håkanson R, Sundler F, Chang K-J. Leu-enkephalin-like material in nerves and enterochromaffin cells in the gut: an immunohistochemical study. Histochemistry 1978; 56:187-96.

12. Lorén I, Alumets J, Håkanson R, Sundler F. Immunoreactive pancreatic polypeptide (PP) occurs in the central and peripheral nervous system: preliminary immunocytochemical observations. Cell Tissue Res 1979; 200:179-86.

13. Lundberg, JM, Hökfelt T, Änggård A, Kimmel JR, Goldstein M, Markey K. Coexistence of an avian pancreatic polypeptide (APP) immunoreactive substance and catecholamines in some peripheral and central neurons. Acta Physiol Scand 1980; 110:107-9.

14. Bevan JA, Bevan RD, Duckles SP. Adrenergic regulation of vascular smooth muscle. In: Bohr DF, Somlyo AD, Sparks HW, Geiger SP, eds. Handbook of physiology. Vol 2. Baltimore: Waverly Press, 1980:515-66.

15. Edvinsson L, Fahrenkrug J, Hanko J, Owman C, Sundler F, Uddman R. VIP nerve supply of intracranial arteries of mammals. Cell Tissue Res 1980; 208:135-42.

16. Edvinsson L, McCulloch J, Uddman R. Substance P: immunohistochemical localization and effect upon cat pial arteries in vitro and in situ. J Physiol 1981; 318:251-8.

17. Uddman R, Alumets J, Edvinsson L, Håkanson R, Sundler F. VIP nerve fibres around peripheral blood vessels. Acta Physiol Scand 1981; 112:65-70.

18. Hökfelt T, Johansson O, Kellerth J-O, et al. Immunohistochemical distribution of substance P. In: von Euler US, Pernow B, eds. Substance P. Nobel Symposium 37. New York: Raven Press, 1977: 117-45.

19. McCulloch J, Edvinsson L. The effects of vasoactive intestinal polypeptide upon pial arteriolar calibre, cerebral blood flow, cerebral oxygen consumption and the electroencephalogram. Am J Physiol 1980; 238:H449-56.

20. Hallberg D, Pernow B. Effect of substance P on various vascular beds in the dog. Acta Physiol Scand 1975; 93:277-85.

21. Leeman SE, Gamse R. Substance P in sensory neurons. TIPS 1981; 2:119-21.

22. Elde R, Hökfelt T, Johansson O, Terenius L. Immunohistochemical studies using antibodies to leucine-enkephalin: initial observations on the nervous system of the rat. Neuroscience 1976; 1:349-51.

23. Fex J, Altschuler RA. Enkephalin-like immunoreactivity of olivocochlear nerve fibers in cochlea of guinea pig and cat. Proc Natl Acad Sci USA 1981; 78:1255-9.

24. Larsson L-I, Sundler F, Håkanson R, Pollock HG, Kimmel JR. Localization of APP, a postulated new hormone, to a pancreatic endocrine cell type. Histochemistry 1974; 42:377-82.

25. Vaillant C, Taylor IL. PP-6-immunoreactivity in nerves and endocrine cells in the mammalian pancreas. In: Basso E, Lezoche E, Speranza V, Walsh JH, eds. Gastrointestinal tract and the adrenal gland. International Symposium on Brain-gut Axis: the New Frontier. Florence: 1981:189.

26. Wilson JG. The nerves and nerve-endings in the membrana tympani. J Comp Neurol 1907; 17:459-67.

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DIAGNOSTIC SIGNIFICANCE OF TRANSTYMPANIC ELECTROCOCHLEOGRAPHY IN MENIÈRE'S DISEASE

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Transtympanic electrocochleography (ECoG) was performed on 32 normal ears, 40 ears affected by hair cell damage without any evidence of endolymphatic hydrops (sensory damage) and 44 ears affected by established Menière's disease. The amplitude of the summating potential (SP) and the amplitude of the action potential (AP) were measured at a click stimulus intensity level of 100 dB HL. The SP amplitude was expressed as a percentage of the AP amplitude. In normal ears, the mean SP/AP ratio was 25% (range 10%-63%). In sensory damage, the SP/AP ratio was 13% (range 0%-29%), and in Menière's ears the SP/AP ratio was 51% (range 29%-89%). In this series, an SP/AP ratio of 29% provided a diagnostic dividing mark between the sensory damage and Menière's-affected ears. Although this precise division was probably fortuitous, it does suggest that ECoG is a useful tool in the differential diagnosis of these two types of cochlear disorders.

INTRODUCTION

Menière's disease remains an etiological and therapeutic enigma. The lack of true animal models and the difficulties in obtaining valid human histological material have hampered research. Nevertheless there is now a reasonable consensus of opinion that the disease is characterized by endolymphatic hydrops[1-3] and that there is relatively little destruction of the sensory elements except perhaps in the apical cochlear turn[2] until the latter stages of the disease.

Transtympanic electrocochleography (ECoG) provides a means of examining the cochlea electrophysiologically and can easily be applied in the study of Menière's disease. Past studies[4-9] have indicated that there is a specific ECoG abnormality seen in ears affected by Menière's disease. Often the ECoG waveform appears wide and distorted. This widening could be interpreted as being due to a relatively large summating potential (SP) component which masks the small action potential (AP). In comparison with other sensory cases, in Menière's disease the SP is large relative to the AP component.

METHODS

There has been some confusion regarding the best method of quantifying the ECoG abnormality seen in Menière's disease. Widening of the SP/AP waveform of over 4 ms was present in 65% of patients tested in one series[5] and provided a means of confirming the diagnosis for these patients. It may be reasonably argued that widening is not a precise measure since it is so dependent on the duration of the acoustic stimulus and that absolute amplitude measurements of the SP and AP should prove more rewarding. However, the absolute amplitudes measured in this series have proved disappointing as far as their diagnostic value is concerned. This was because the amplitudes showed considerable variation depending, presumably, on the electrode location and impedance. In the series of purely sensory damaged ears, two standard deviations above the mean SP amplitude was calculated to be 4.26 μV. Only 36% of the Menière's ears (40-80 dB HL) tested had absolute SP amplitudes exceeding 4.25 μV.

As it was readily apparent that the smaller SP amplitudes tended to occur with the smaller AP amplitudes, the results were analyzed in terms of the ratio of the SP amplitude to the AP amplitude (peak to peak). Using this method of analysis, a highly significant difference emerged between the sensory group and the Menière's group with hearing losses between 40-80 dB HL (mean of 2-4 kHz). An SP/AP ratio value of 29% clearly divides the two groups so that using a criterion of 30% or greater, 94% of the Menière's group were correctly identified with no false-positives.

The SP/AP ratio was also examined for patients with Menière's disease but with hearing better than 40 dB and the results were compared to a normal group. Unfortunately no statistical difference was seen between the two groups.

Patients with hearing losses greater than 80 dB HL were not included in this analysis.

Fifty ears with clinically obvious Menière's disease were studied. In every case, the ear tested was judged to be in an "active" stage of the disease; the hearing was affected and there had been at least two attacks of rotational vertigo with nausea during the preceding one month. Six ears were excluded because the hearing level exceeded 80 dB HL (2-4 kHz average). Of the remaining 44 ears, 11 ears had comparatively normal high-frequency hearing (less than 40 dB HL, 2-4 kHz) and 33 ears had a hearing loss from 40-80 dB HL (2-4 kHz).

The normal control group (32 ears) did not include any of the "normal" ears of the Menière's patients, as several such recordings have shown unexpectedly large SP/AP ratios despite apparently normal cochlear and labyrinthine function. While this finding is interesting, its significance is unknown. There are some obvious problems in obtaining normal controls for transtympanic ECoG studies. The control group consisted of 16 ears of children tested for threshold purposes, three ears of adults with nonorganic hearing loss and 13 other adults tested for various other reasons. Normally we do not advocate the use of transtympanic ECoG for the detection of nonorganic hearing loss but two patients were suspected of having an acoustic neuroma and one patient was tested unsuspectingly. The mean age of the normal group was 20.3 years, which was younger than the Menière's group (44 years) and the sensory group (52 years). (Sensory group refers to those ears tested that had pure hair cell pathology without any clinical evidence of endolymphatic hydrops.) No statistical dif-

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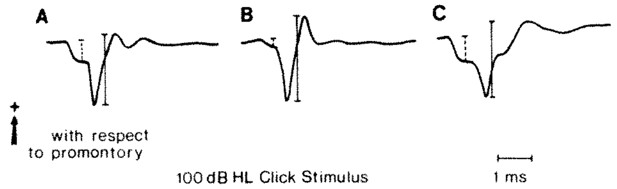

Fig. 1. Method of measuring SP (dotted line) and AP (solid line) amplitudes in recordings of A) typical normal, B) typical "pure" sensory damage (hair cell loss), and C) typical Menière's disease (endolymphatic hydrops).

ference between the SP/AP values was noted between the normal children and the normal adults.

The sensory group (40 ears) with pure sensory hearing damage had a hearing loss from 40-80 dB HL (2-4 kHz). Several ears had to be excluded because the hearing exceeded 80 dB HL. This group consisted mainly of ears affected by acoustic trauma, ototoxic agents and vascular lesions. Ears affected by syphilis and sudden hearing loss were not included because of their possible association with endolymphatic hydrops. The mean hearing loss, 2-4 kHz average, was 64 dB (SD 14.06), which was greater than the Menière's group (56-82 dB, SD 1.2-11).

Fourteen of the Menière's ears and the majority of the normal and the sensory ears were tested using the standard Medelec/Amplaid Mk III apparatus. The remainder were tested using similar recording amplifiers and stimulus apparatus but the responses were averaged on a minicomputer (CA1 Alpha LS 12-20).

All recordings were made using standard silver/silver chloride electrodes placed on the forehead or chin (earth) and the ipsilateral mastoid (reference). The active electrode was a thin stainless steel wire which was insulated with Teflon except for the tip and pierced the tympanic membrane to rest on the promontory close to the round window niche. No local anesthesia was used in the majority of patients and a few patients had local anesthesia using iontophoresis. No sedatives were used. Only one patient found the procedure upsetting although she did allow the recording to proceed. The procedure appears to be very safe if performed competently; one of us (WPRG) has now performed transtympanic ECoG since 1973 on over 3,000 ears, with only two known complications: one patient complained that his trigeminal neuralgia was worse for two months following ECoG and another complained that his tinnitus became louder.

The recording amplifiers had a band pass of 3.2 Hz to 3.2 kHz with a slope of 12 dB per octave. The stimulus was a 100 μs click delivered from a screened TDH 39 headphone which was clamped magnetically to a special ring support placed around the test ear. Further details have been published.[10] The stimulus intensity was 100 dB HL, the reference zero having been calibrated using otologically normal, young volunteers. Each averaged response represented the responses to 512 stimuli and the test was repeated for all conditions to check the reliability of the response.

The method of measuring the amplitude of the SP and AP is shown in Figure 1. The cochlear microphonic was measured at its maximum peak-to-peak value.

RESULTS

Normal Ears (0-20 dB HL). The normal ears yielded a wide range of AP amplitudes varying from 1.9-51 μV with a mean of 17.61 (SD 12.38) and the SP also varied from 0.5-10μV with a mean of 3.9 (SD 2.66). The SP/AP amplitude varied in normal subjects from 10%-63%, with a mean of 25% and SD of 14 (Table 1).

Menière's Group (0-40 dB HL). The absolute values of the AP and SP varied a great deal, as in all other groups studied. The AP values (range 2.5-34 μV, mean 13.06, SD 10.09) were slightly lower than the normal group (range 1.9-51 μV, mean 17.61, SD 12.38) and the SP values (range 0-10μV, mean 4.61, SD 4.46) were slightly greater than normal. The mean SP/AP ratio (35%) was also slightly larger but statistical analysis failed to show a significant difference between the normal group and the Menière's group with hearing better than 40 dB HL.

Sensory Group (40-80 dB HL). The AP values tended to be smaller than the normal group but were commensurate with the Menière's group with equivalent hearing loss. Although cochlear microphonic (CM) is not the subject of this paper it may be noted that, in general, smaller CM values were observed in this group than in the other groups (> 2 μV), but the great variation in size (one patient actually had the largest CM of the series) limits the diagnostic value of the CM. The SP/AP ratio in this group varied from 0%-29%, with a mean of 13% (SD 9).

Menière's Group (40-80 dB HL). The SP/AP ratio in this group varied from 29%-89% and clearly separates the recordings from those obtained from the sensory group. The "watershed" of 29% seemed fortuitous but the data have now been analyzed several times and there does not appear to be any bias in selection. The CM amplitudes were similar to the normal group and this finding is consistent with Schmidt et al[11] who suggested that it was related to the preservation of the hair cells in the basal coil of the cochlea.

Comparison Between Groups. When normal subjects were compared with the Menière's group (0-40 dB HL), no significant differences between the

TABLE 1. AMPLITUDE VARIATIONS OF ELECTROCOCHLEOGRAPHIC COMPONENTS FOR DIFFERENT GROUPS OF SUBJECTS

	Normal (0 - 20 dB HL) (n = 32)			*Menière's (0 - 40 dB HL) (n = 11)*			*Sensory* (40 - 80 dB HL) (n = 40)*			*Menière's (40 - 80 dB HL) (n = 33)*		
	Range	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	*Mean*	*SD*	*Range*	*Mean*	*SD*
AP (μV)	1.9-51	17.61	12.38	2.5-34	13.06	10.09	0.7-30	7.03	6.41	3.00-30	8.12	6.27
SP (μV)	0.5-10	3.90	2.66	0.0-10	4.61	4.46	0.0-8	1.12	1.52	1.25-18	3.92	3.34
CM (μV)	2.2-17	8.92	4.29	—	—	—	0.3-20	6.73	4.60	2.10-17	7.08	4.44
SP/AP Ratio (%)	10.0-63	25.03	13.70	0.0-59	35.27	21.55	0.0-29	12.78	9.23	29.40-89	51.22	16.15

*Ears with pure hair cell pathology but without clinical evidence of endolymphatic hydrops.

AP - Action potential, SP - Summating potential, CM - Cochlear microphonic.

TABLE 2. SIGNIFICANCE LEVELS FOR COMPARISONS BETWEEN GROUPS

	AP ("d" value)[12]	SP ("d" value)[12]	SP/AP Ratio (Mann-Whitney test)
Normal/Menière's (0-40 dB HL)	NS (1.60)	NS (0.31)	NS
Sensory/Menière's (40-80 dB HL)	NS (0.73)	1% (4.34)	1%

NS - Not significant.

mean values of the absolute AP amplitudes, the absolute SP amplitudes or the SP/AP ratios were detected using the Fisher-Behrens "d" statistic[12] and the Mann-Whitney test (Table 2).

Comparison of the Menière's group with a hearing loss from 40-80 dB HL with the sensory group with similar hearing loss showed no significant difference between the mean values of absolute AP amplitudes. The important finding was a significant difference at the 1% level between both the mean values of the absolute SP amplitudes and the SP/AP ratios.

DISCUSSION

The significant finding was that the SP/AP ratio was clearly different between the Menière's ears and those affected purely by hair cell loss, providing that there was at least a 40 dB high-frequency hearing loss. Eggermont and colleagues[9-11] maintain that the SP in Menière's ears is of comparable magnitude to that in normal ears, and, since SP depends on the presence of hair cells, that the SP seen in Menière's ears indicated survival of the hair cells in this condition. Nevertheless there was a distinct clinical impression that larger SP amplitudes were obtained from patients during "active periods" when their hearing was poor.[13] Furthermore, glycerol dehydration studies have shown a consistent SP decrease in patients who had a hearing gain.[6] It is not possible to explain these findings by the hair cell survival theory alone and some relation to the presence of endolymphatic hydrops seems probable.

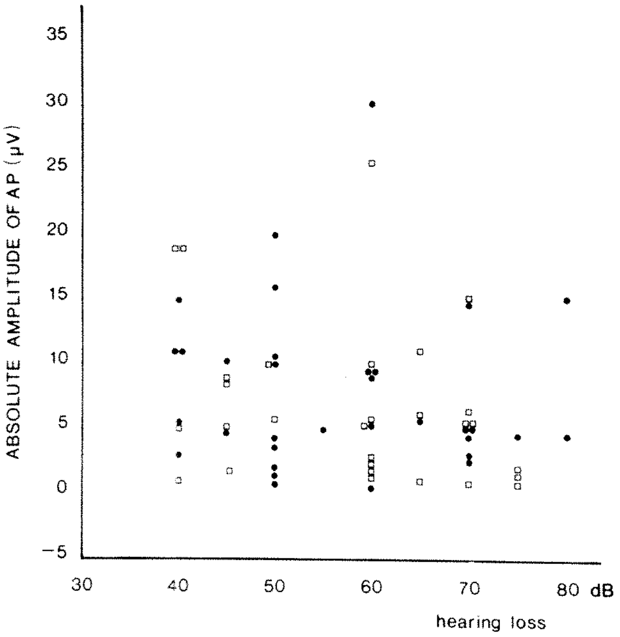

Fig. 2. Measurements of absolute AP amplitude v hearing loss in Menière's (●) and sensory (□) groups.

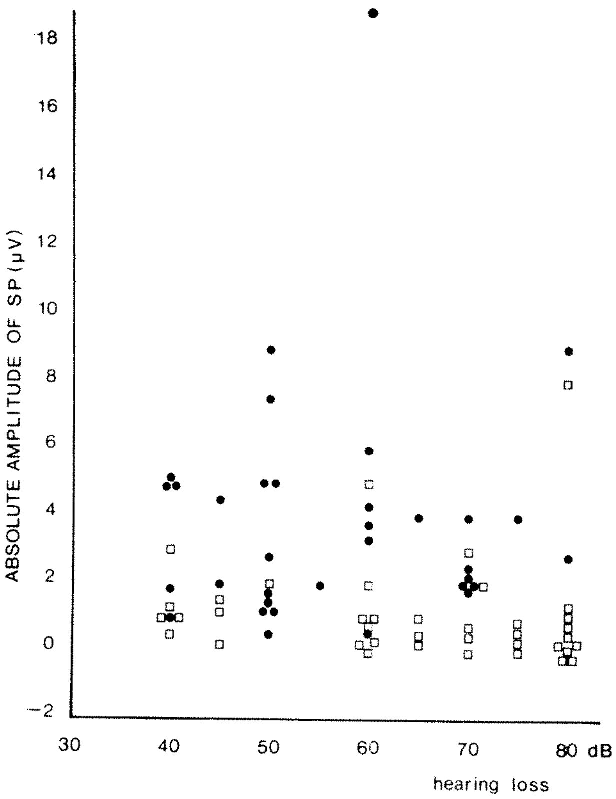

Fig. 3. Measurements of absolute SP amplitude v hearing loss in Menière's (●) and sensory (□) groups.

In an attempt to resolve these differences, a careful analysis of our data was undertaken. Although there is wide scatter among the absolute AP amplitudes (Fig. 2) it is fairly clear that a decrement in AP amplitude occurs with increasing hearing loss in both the Menière's and sensory groups. No significant differences between the groups were found at any hearing level (Table 2).

Comparison of the SP amplitudes with hearing loss in each group revealed a decrement in SP amplitude with increasing hearing loss in the sensory group but not in the Menière's group (Fig. 3). The lack of change in SP amplitude despite increasingly severe hearing loss is clearly the factor responsible for the large SP/AP ratio noted in Menière's disease. Indeed the SP/AP ratio (Fig. 4) appears to increase as the hearing loss becomes more profound in the Menière's group, whereas it decreases in the sensory group. Further statistical analysis (Fig. 5) confirms that the diagnostic significance of the SP/AP ratio in Menière's disease increases as the patient suffers from increasingly severe high-frequency loss.

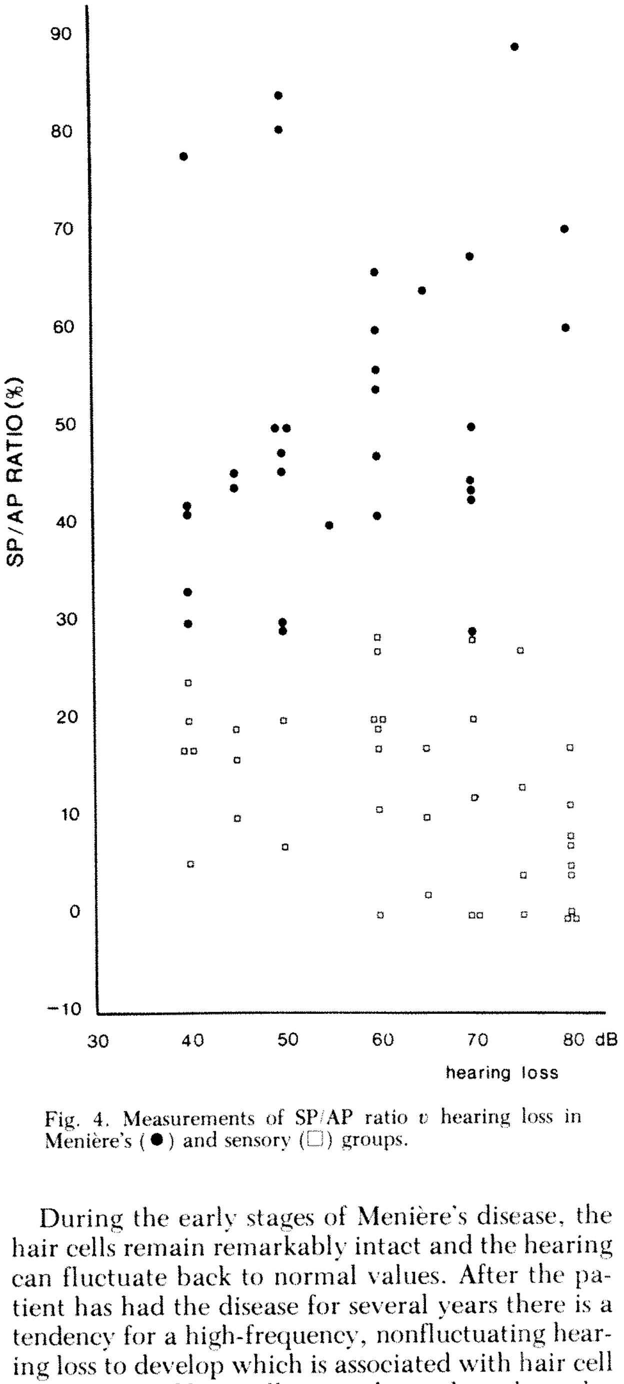

Fig. 4. Measurements of SP/AP ratio *v* hearing loss in Menière's (●) and sensory (☐) groups.

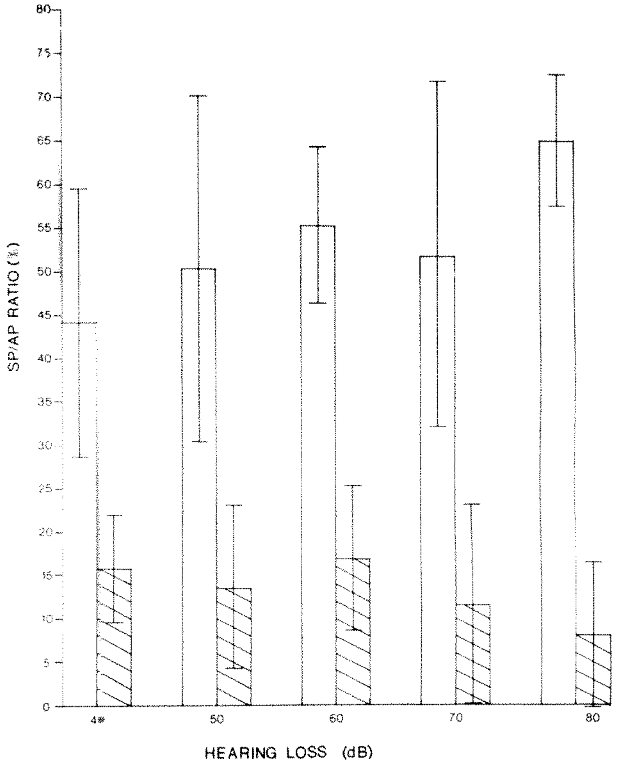

Fig. 5. Significance of SP/AP ratio at different hearing levels in Menière's (☐) and sensory (▨) groups.

During the early stages of Menière's disease, the hair cells remain remarkably intact and the hearing can fluctuate back to normal values. After the patient has had the disease for several years there is a tendency for a high-frequency, nonfluctuating hearing loss to develop which is associated with hair cell destruction. If hair cell survival was the only explanation for the SP, then a decrement in SP amplitude with increasing hearing loss should have been seen in the Menière's group and the diagnostic significance of the SP/AP ratio reduced with hearing losses exceeding 60 dB HL.

An alternative hypothesis is that the SP amplitudes in Menière's disease reflect both the survival of hair cells and an increase in the distortion of the potentials they produce. With increasing hearing loss, there is a loss of hair cells in the Menière's ears but the asymmetry of the basilar membrane caused by the endolymphatic hydrops leads to the remaining hair cells generating greater receptor potentials than normal. As a result the SP amplitude is increased to near normal levels.

In summary, the significant finding is that the SP/AP ratio obtained by transtympanic ECoG can usefully be employed in the differential diagnosis of Menière's disease and pure hair cell pathology providing the hearing loss exceeds 40 dB (averaged 2-4 kHz). This conclusion is consistent with Coats[7] and Kumagami et al.[14]

REFERENCES

1. Hallpike CS, Cairns H. Observations on the pathology of Meniere's syndrome. J Laryngol Otol 1938; 53:620-55.

2. Schuknecht HF. Pathology of the ear. Cambridge: Harvard University Press, 1974:453-65.

3. Antoli-Candella F Jr. The histopathology of Meniere's disease. Acta Otolaryngol (Stockh) 1976; Suppl 340:1-42.

4. Gibson WPR, Ramsden RT, Moffat DA. Clinical electrocochleography in the diagnosis and management of Meniere's disease. Audiology 1977; 16:389-401.

5. Gibson WPR. Clinical electrocochleography: the significance of the summating potential in Meniere's disease. In: Barber C, ed. Evoked potentials. Lancaster: MTP Press Ltd, 1980: 347-52.

6. Moffat DA, Gibson WPR, Ramsden RT, Morrison AW, Booth JB. Transtympanic electrocochleography during glycerol dehydration. Acta Otolaryngol (Stockh) 1978; 85:158-66.

7. Coats AC. The summating potential and Meniere's disease. I. Summating potential amplitude in Meniere and non-Meniere ears. Arch Otolaryngol 1981; 107:199-208.

8. Gibson WPR. Essentials of clinical electric response audiometry. Edinburgh: Churchill Livingstone; 1978:87-93.

9. Eggermont JJ. Summating potentials in Meniere's disease. Arch Otolaryngol 1979; 222:63-75.

10. Ramsden RT, Gibson WPR, Moffat DA. Anaesthesia of the tympanic membrane using iontophoresis. J Laryngol Otol 1977; 91:779-85.

11. Schmidt PH, Eggermont JJ, Odenthal DW. Electrocochleographic study of Meniere's disease. Acta Otolaryngol (Stockh) 1974; Suppl 316:75-84.

12. Campbell RC, ed. Statistics for biologists. Cambridge: Cambridge University Press, 1967.

13. Moffat DA. Transtympanic electrocochleography in Meniere's disease: variation in the amplitude of the summating potential related to clinical status. Br J Audiol 1979; 13:149-52.

14. Kumagami H, Nishida H, Moriuchi H. Changes of the action potential, the summating and cochlear microphonics in experimental hydrops. ORL J Otorhinolaryngol Relat Spec 1981; 43:314-27.

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TENTH ANNUAL MEETING OF AMERICAN AUDITORY SOCIETY

The American Auditory Society announces its Tenth Annual Meeting to be held in Cincinnati, Ohio, on November 17, 1983, the day before the Annual Convention of the American Speech-Language-Hearing Association. The theme of the meeting will be "A Decade of Progress." Persons interested in the ear and hearing are invited to submit papers to be considered for presentation. Five copies of a 300-word abstract with a brief summary should be submitted by June 1, 1983, to Robert W. Keith, PhD, Department of Otolaryngology, University of Cincinnati Medical Center, Mail Location #528, Cincinnati, Ohio 45267. Any questions about the meeting can be directed to the same address.

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WORLD CONGRESS OF OTORHINOLARYNGOLOGY

The XIIIth World Congress of Otorhinolaryngology will be held in Miami Beach May 26 — June 1, 1985. For further information please contact Anthony J. Maniglia, MD, Secretary-General, P.O. Box 016960 (D-48), Miami, FL 33101.

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MESODERMAL INDUCTION DEFECT AS A POSSIBLE CAUSE OF EAR MALFORMATIONS

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Deafness due to inner ear anomalies is rarely associated with malformations of the auricles. We describe two brothers with profound congenital sensorineural deafness, abnormal vestibular function, normal ossicles, and delayed motor development. Since the external and inner ear originate from distinctly separate structures, the embryogenesis of this malformation association is less clear than in the more common association of external and middle anomalies, where the latter two structures are derived from the first and second branchial arches. The combination of auricular and inner ear anomalies, with sparing of the middle ear structures, can be explained on the assumption that mesodermal induction is responsible for normal differentiation of both the otocyst and of the branchial arch ectoderm. A recessive mutant gene may lead to a deficiency of a mesodermal inducer substance of a target tissue receptor site. A similar mechanism may be involved in other multiple malformation syndromes, whereby a mutant gene acting during a specific period of organogenesis causes disruption of the normal induction-competence relationship.

INTRODUCTION

The existence of multiple causes of congenital deafness reflects the complexity of the anatomy and physiology of the ear. Ear anomalies are classified into external, middle and inner ear defects, or combinations thereof, with or without involvement of extra-auditory structures. By far, the majority of genetic deafness syndromes are inherited as dominant or recessive mendelian traits, with varible degrees of expressivity. There are a number of possible explanations to account for multisystem abnormalities associated with a large proportion of genetic deafness syndromes.

Pleiotropic Effect of A Single Mutant Gene.[1] For example, in craniofacial and skeletal dysplasias, deafness may be due to abnormal ossicular formation as part of a more generalized bony defect, or may be due to abnormal formation of ear structures caused by external constraints imposed by the abnormal formation of the temporal bone.[2] The accumulation of metabolites within the ear structures can interfere with hearing in storage diseases.[2,3] In conditions such as Alport's syndrome,[2,4] Usher's syndrome,[2,5] Jervell and Lange-Nielsen syndrome,[2,3] and Pendred's syndrome,[2] the observed histopathology of the multisystem organ involvement is suggestive of a metabolic defect, although the exact nature of the defect is presently unknown.

Fortuitous Association of Two Mutant Genes. Fraser[1] has proposed two separate mutant genes segregating together, one causing deafness and the second, other anomalies, as a possible mechanism in dominant pulmonic stenosis and recessive albinism. Patients with a fortuitous association of autosomal recessive deafness and autosomal dominant characteristics have also been reported.

Undetectable Chromosomal Abnormalities.[1] Dominantly inherited multiple malformation syndromes may be due to deletions or duplications of more than one base pair, even though such abnormalities are not detectable by conventional karyotype analysis. Fraser has suggested that complex recessive malformation syndromes such as cryptophthalmos may represent the homozygous state of such small chromosomal abnormalities.

A defect in embryonic induction may be an additional mechanism responsible in some cases of deafness associated with anomalies of seemingly unrelated structures. Embryonic induction is a well-established concept which implies the existence of an accurately synchronized system of intercellular communication which directs the differentiation of predestined groups of cells into distinct organs. That a specific group of cells is predestined to differentiate into specific anatomic structures was elegantly demonstrated by Nakamura et al,[6] where the fate of each cell in a 32-cell stage embryo was traced. The migration and differentiation of these embryonic cells is under the direct influences of inducer substances or organizers. Evidence of their existence was first provided by the experiments of Spemann and Mangold.[7] In the patients presented here, it is proposed that their unusual pattern of ear anomalies is consistent with an impaired induction mechanism.

CASE REPORTS

Case 1. This male patient was born to a G_4P_3 23-year-old mother and a 30-year-old father. Pregnancy, labor and delivery were uneventful. Birth weight was 3,920 g. Except for malformed external ears and right facial palsy, no problems were encountered during the immediate postnatal period. During the first three months of life, it was noted that he was hypotonic and failed

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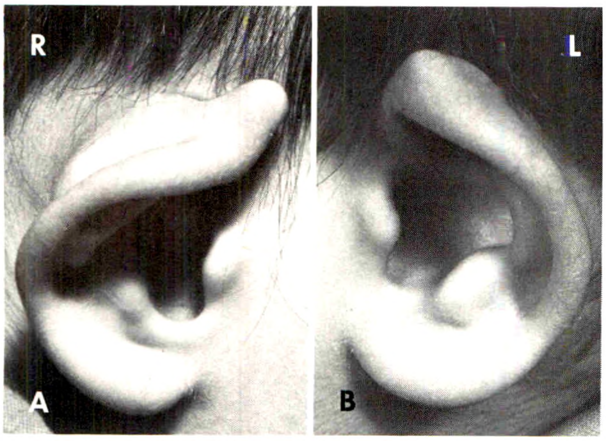

Fig 1. (Case 1) A) Right and B) left auricles. Note thick cupped helices.

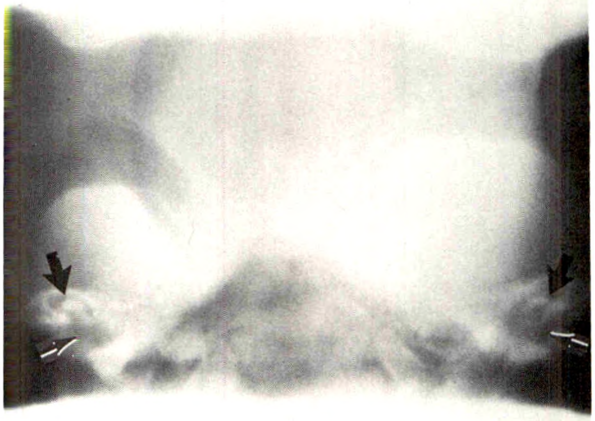

Fig 2. (Case 1) Left and right AP view temporal bone laminograms. Large arrows indicate normal-appearing ossicular chain. Small arrows indicate external auditory canals. Internal auditory canals, cochleas, and vestibular apparati are absent.

to develop adequate head control. The right facial palsy persisted and deafness was suspected due to his failure to attend to sounds. His motor developmental milestones were markedly delayed. At 12 months of age, he was unable to sit or walk. A functional heart murmur was detected at age 3 months. His health has otherwise remained good. His weight and head circumference remained appropriate. The family history is significant in that his parents are first cousins, and his older brother (case 2) is also deaf, developmentally delayed and has abnormal external ears.

Physical examination performed at 5 months of age revealed normal growth parameters. He attended to visual stimuli and smiled, but showed no response to loud noises. He was markedly hypotonic with poor head control and laid in a frog-leg position, but actively moved all extremities. He failed to bear weight on his legs and a stepping response was absent. He was unable to roll over. He had markedly diminished movement of the right facial muscles, and the right eye failed to close on crying. The extraocular eye movements were intact and fixation nystagmus was present. His head was brachycephalic with a prominent forehead. There were no cataracts or retinal abnormalities. The ears (Fig 1) were low set and dysplastic with cupped, pointed helices. The external auditory canals were patent but narrow, and the tympanic membranes had a normal appearance. There was no thyroid gland enlargement. A grade 2/6 systolic murmur was heard at the left midsternal border. The remainder of the examination was normal.

Audiometric studies revealed profound bilateral sensorineural deafness with virtual absence of response over a frequency range of 200-5,000 Hz. The stapedial reflex was absent bilaterally. Caloric stimulation failed to elicit nystagmus bilaterally. Temporal bone laminograms (Fig 2) revealed the ossicular chains to be present with no detectable abnormalities. The internal auditory canals, cochleas, and vestibular apparati were absent. Computerized tomography of the brain demonstrated moderate enlargement of the ventricles and basilar and subarachnoid cisterns with narrowing of the brainstem. A chest x-ray study and EKG were normal. The G-banded karyotype was normal. Complete blood cell count (CBC), urinalysis, thyroxine (T_4) and thyroid stimulating hormone (TSH) results were also normal.

Case 2. This patient is the $4\frac{1}{2}$-year-old brother of the proband (case 1). Pregnancy, labor and delivery were uncomplicated. Profound deafness was diagnosed in early infancy, and his motor development was markedly delayed. He began to walk at age 3. He presently attends a school for the deaf but functions at a decreased level of intelligence, even when his deafness is considered. His general health is good and physical growth parameters are age-appropriate.

Physical examination reveals ear anomalies similar (Fig 3) to those of his brother, but somewhat less pronounced. There was no nystagmus or facial asymmetry. The optic fundi appeared normal. He had good muscle tone but his gait and gross and fine motor movements were somewhat clumsy. His external auditory canals and tympanic membranes were normal in appearance. There was no fixation nystagmus, and reflex nystagmus was not elicited by caloric stimulation. The thyroid was not enlarged. His heart rate was regular and there was no heart murmur. The remainder of his examination was normal. His parents and two other brothers are unaffected.

Audiometric studies revealed profound sensorineural deafness. Hearing sensitivity was estimated to be at the same level as in the brother (case 1). Skull laminograms (Figs 4-6) revealed absence of cochleas and severely malformed vestibular and semicircular canals. The ossicles appeared normal. At age 4 years 1 month his cognitive nonverbal skill development, tested by the Johnson Nonverbal Performance Scale, was at a 3 to 3.5-year-old level.

DISCUSSION

Over 140 genetic and metabolic causes of deafness are documented by Konigsmark and Gorlin,[3] and summarized in the Table.[8] The majority of these cases are sensorineural deafness (65%) and are rarely associated with auricular malformations (1.4%), whereas if a conductive component is present, with or without a neural component, associated auricular abnormalities are much more likely to be encountered (12%). Conversely, if the auricles are

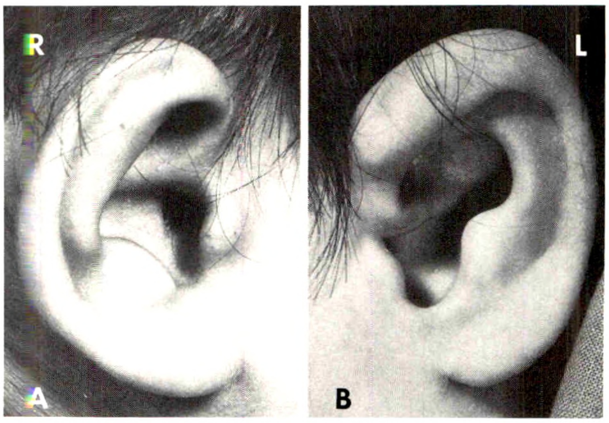

Fig 3. (Case 2) A) Right and B) left auricles. Helices are thick and folded, but to lesser extent than those of brother (Fig 1).

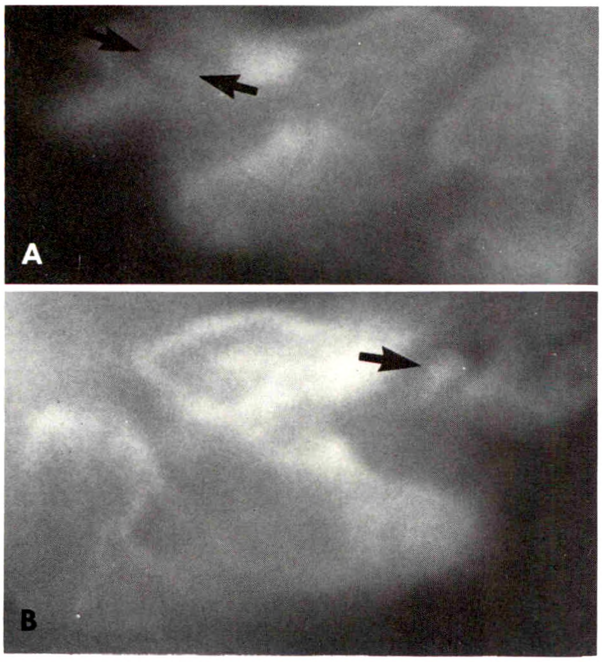

Fig 4. (Case 2) A) Right and B) left AP view temporal bone laminograms. Normal ossicles are indicated by arrows.

malformed, a conductive defect is more likely present, while a sensorineural defect is more likely to be present if the auricles are normal.

As can be seen from the Table of the genetic causes of sensorineural deafness, only two of 92 (2.3%) are associated with malformed auricles. The patients presented in this report are an example of the uncommon association of auricular and inner ear malformations with sparing of the middle ear. This association also occurs in trisomy 18[3] and in the syndrome of sensorineural deafness with preauricular pits and branchial fistulas.[3] The origin of this type of malformation association is not as readily explainable as in the condition where auricular and middle ear malformations occur together, with sparing of the inner ear. For example, in syndromes of first and second branchial arch malformations, it is common to encounter auricular and middle ear anomalies together, usually with normal inner ear structures.[9] The embryogenesis of such an association is explained by the auricles and ossicles all being derived from the first and second branchial arches. The fact that the inner ear is intact in such syndromes is thought to be due to its origin in the auditory placode, which is anatomically distinct from the branchial arches and presumably develops independently of them.

A mechanism by which auricular and inner ear anomalies can occur together can be formulated on the basis of the work of Yntema.[10] His studies of inner ear development in amphibians have shown that normal development of the inner ear is dependent on the inductive influence of the chorda-mesoderm and the neural tube. Initial differentiation of the ear is directed by the induction of the chorda-mesoderm, which comes to lie beneath it during the late gastrular stage. As neural tube closure approaches completion (week 4), the mesodermal inductive influence begins to wane, and further induction of the ear ectoderm is effected by the neural tube which is adjacent to it during the neurulation period. Under the influence of this neural induction, the otic placode appears and proceeds to form the otocyst, which migrates medially towards the rhombencephalon. The cochlea, utricle, saccule and semicircular canals all originate from the otocyst.

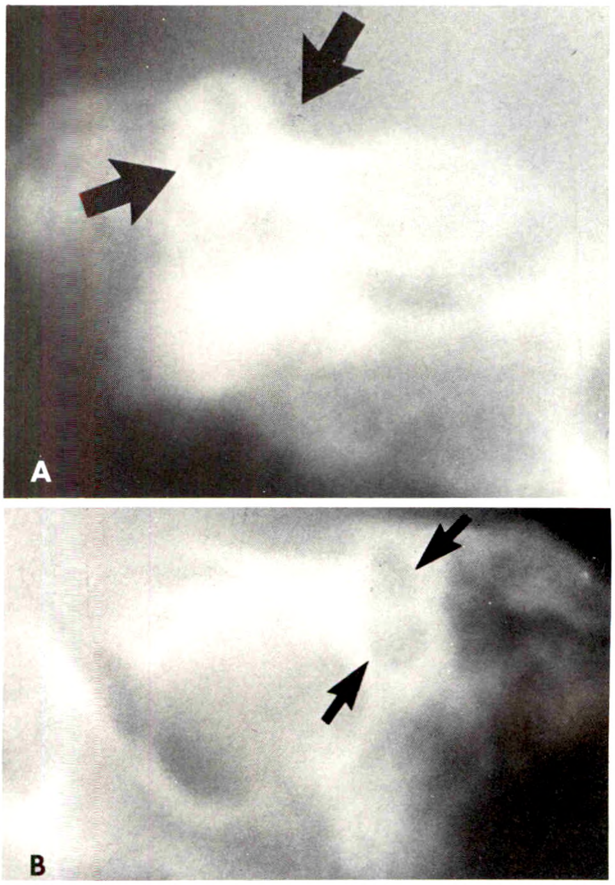

Fig 5. (Case 2) A) Right and B) left AP view temporal bone laminograms. Arrows point to abnormally structured, dilated semicircular canals.

Yntema has shown that for normal induction to occur, the inductive influence on the target tissue must occur in synchrony with the ability of the target tissue to respond to induction (competence). The peak of the competence period precedes the peak of the induction period, both for mesodermal and neural induction.

While the otocyst is differentiating under the influence of mesodermal and neural induction, the auricle is being formed from the six auricular hillocks, which appear as swellings on each side of the first branchial groove. The major portion of the auricle is formed from the second arch giving rise to the helix, anthelix, antitragus, and lobule while the first arch forms the tragus and part of the helix.

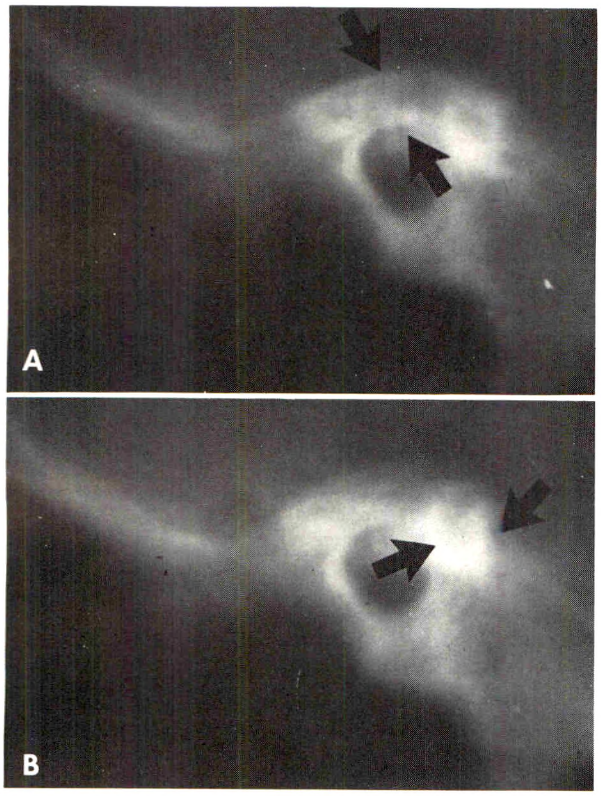

Fig 6. (Case 2) Temporal bone laminograms, right lateral projection. Arrows indicate A) normal ossicles and B) abnormal semicircular canals.

Although the inner ear differentiates in response to mesodermal and neural induction, the structures which induce the development of the auricles have not been identified. On the assumption that the auricles also develop, at least in part, in response to mesodermal induction, a model can be proposed explaining the malformation pattern in our patients. The patients in this report have absence of inner ear structures, or at best, rudimentary structures, a type of abnormality first described by Michel.[8] A defect of this kind could have resulted from failure of the otocyst to differentiate very early in its course, coincident with the period of mesodermal induction. The auricles in our patients, although malformed, are comparatively less severely affected than the inner ear, strongly suggesting that factors in addition to mesodermal induction play a prominent role in their development. Based on the above observations, the following mechanisms may explain the pattern of the ear anomalies in our patients:

1. *Deficient Action of An Inducer Substance.* If one assumes that a mutant gene is responsible for the production of a defective mesodermal inducer substance, the result can be early failure of the otic placode and auricular hillocks to differentiate normally. Since both the otic placode and auricular hillocks are of ectodermal origin, while the ossicles originate from branchial arch mesoderm, one may conclude the defective inducer substance exerts specific action on certain structures of ectodermal origin. On the other hand, production of a defective neural inducer may cause conditions where the structures are all present, but malformed, representing an induction defect during a later stage of ear devemopment. Furthermore, the mesodermal induction defect may also be responsible for the brainstem defect identified in the first patient. Evidence that mesodermal induction plays a role in the regional differentiation of the neural axis has been provided by Saxon and other investigators.[11]

GENETIC CAUSES OF DEAFNESS CLASSIFIED BY TYPE AND ASSOCIATION WITH MALFORMATION OF AURICLES[8]

Type	*Cases* *No.*	*%*	*Auricles Malformed* *No.*	*%*	*Auricles Normal* *No.*	*%*
Sensorineural	92	64.8	2	1.41	90	63.4
Conductive	21	14.8	9	6.35	12	8.4
Mixed	29	20.4	8	5.64	21	14.8
	142	100.00	19	13.40	123	86.6

2. *Deficient Competence of Target Tissues.* The competence of a target tissue is determined by the action of the inducer substance possibly by means of its recognition and interaction with a cell surface receptor. If this cell surface receptor were to be altered in its structure, the competence of the target tissue could be compromised, rendering it unresponsive to the action of the inducer substance, resulting in incomplete or abnormal differentiation. A known analogy to such a situation is seen in the testicular feminization syndrome, which is due to unresponsiveness of target tissues to androgens. Thus, impaired competence of ectodermal tissues from which the otic placode and auricular hillocks develop can be responsible for the malformations present in our patients. Another possibility is that the competence itself is not altered, but that its peak period is out of phase with the inducer effect. This timing error would result in the same malformation complex.

The mechanism proposed here attempts to link the existence of malformations of several anatomic structures which are presumed to form independently of one another to a common source. In this case a mutant recessive gene, which produces either a defective mesodermal inducing factor or possibly a defective cell surface recognition factor, is the probable cause. Although inducer substances have not been isolated from human tissues, the polypeptide nature of inducing factors was demonstrated by Tiedemann et al,[12] who succeeded in extracting mesodermal and neural inducting factors from animal tissues and subjecting them to inactivation by the proteolytic enzymes. Other investigators[11] succeeded in isolating, in pure form, the CNS "mesodermalizing" factor from avian and amphibian embryos. It has also been shown[11] that some inducing factors exert their action over considerable distances with no dependence on intercellular contact, while other classes of inducing factors have a local effect requiring intercellular contact. The former inducing mechanism is exemplified in the process of embryonic sex differentiation, where androgens produced by the embryonic testis exert their effect on the urogenital sinus in inducing the development of male external genitalia. A known example of the latter mechanism is present in the formation of the kidney, where the metanephrogenic mesenchyme is induced to form nephrons by the ureteric bud. Recently, is has also been shown that cytoplasmic processes from the spinal cord extend into the metanephrogenic mesenchyme, and are instrumental in the induction of tubule differentiation.[13] Renal dysplasias may, therefore, represent a defect in local induction. In the thalidomide embryopathy, where the anomalies are very likely due to impaired induction of limb development, auricular anomalies and a Michel-type inner ear defect have also been described.[14]

SUMMARY

The association of extra-auditory anomalies in genetic deafness syndromes has generally been attributed to pleiotrophy, fortuitous association of more than one mutant gene, or a chromosome defect not detectable by present techniques. It is proposed that an additional mechanism can be a defect of induction during embryogenesis. In the patients presented in this paper, we applied this concept to explain their pattern of malformations in the light of the present state of knowledge of embryonic induction. This concept can be applied to various other multiple malformation syndromes whereby a mutant gene, acting during a specific period of organogenesis, is responsible for disruption of the normal induction-competence relationship.

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REFERENCES

1. Fraser GR. Profound childhood deafness. J Med Genet 1964; 1:118-51.

2. Friedman I. Pathology of the ear. Oxford: Blackwell Scientific Publications, 1974:359-61, 363-4, 368-9, 371-80, 385-6.

3. Konigsmark BW, Gorlin RJ. Genetic and metabolic deafness. Philadelphia: WB Saunders, 1976:xv-xx, 56, 345-8, 357-9, 368.

4. Spears GS. Alport's syndrome: a consideration of pathogenesis. Clin Nephrol 1973; 1:336-7.

5. Sandra L, Davenport H, O'Nuallain S, Omenn GS, Wilkus RJ. Usher syndrome in four hard of hearing siblings. Pediatrics 1978; 62:578-82.

6. Nakamura O, Takasaki H, Nagata A. Further studies of the prospective fates of blastomeres at the 32-cell stage of Xenopus laevis embryos. Med Biol 1978; 56:355-60.

7. Spemann H, Mangold H. Über Induction von Embryoanalanalgen durch Implantation artfemder Organizatoren. Arch Mikr Anat Entwmech 1924; 100:599.

8. Michel EM. Memoirs sue les anomalies congenitales de l'oreille interne. Gas Méd Strasburg 1863; 3:55.

9. Karmody CS, Feingold M. Autosomal dominant first and second branchial arch syndrome. In: Bergsma D, Feingold M, Sydney GS, Greene SC, eds. Malformation syndromes. Birth defects: original article series. New York: The National Foundation March of Dimes, 1974:31-40.

10. Yntema CL. An analysis of induction of the ear from foreign ectoderm in the salamander embryo. J. Exp Zool 1950; 113:211-43.

11. Saxén L. Two-gradient hypothesis of primary embryonic induction. Med Biol 1978; 56:293-8.

12. Tiedemann H, Kesserling K. Becker U. The chemical nature of organ determining substances in the early development of embryos. Biochim Biophys Acta 1961; 49:603.

13. Tarin D. Embryonic induction. Med Biol 1978; 56:380-5.

14. Jørgensen MB, Kristensen HK, Buch NH. Thalidomide induced aplasia of the inner ear. J Laryngol Otol 1964; 78: 1095-101.

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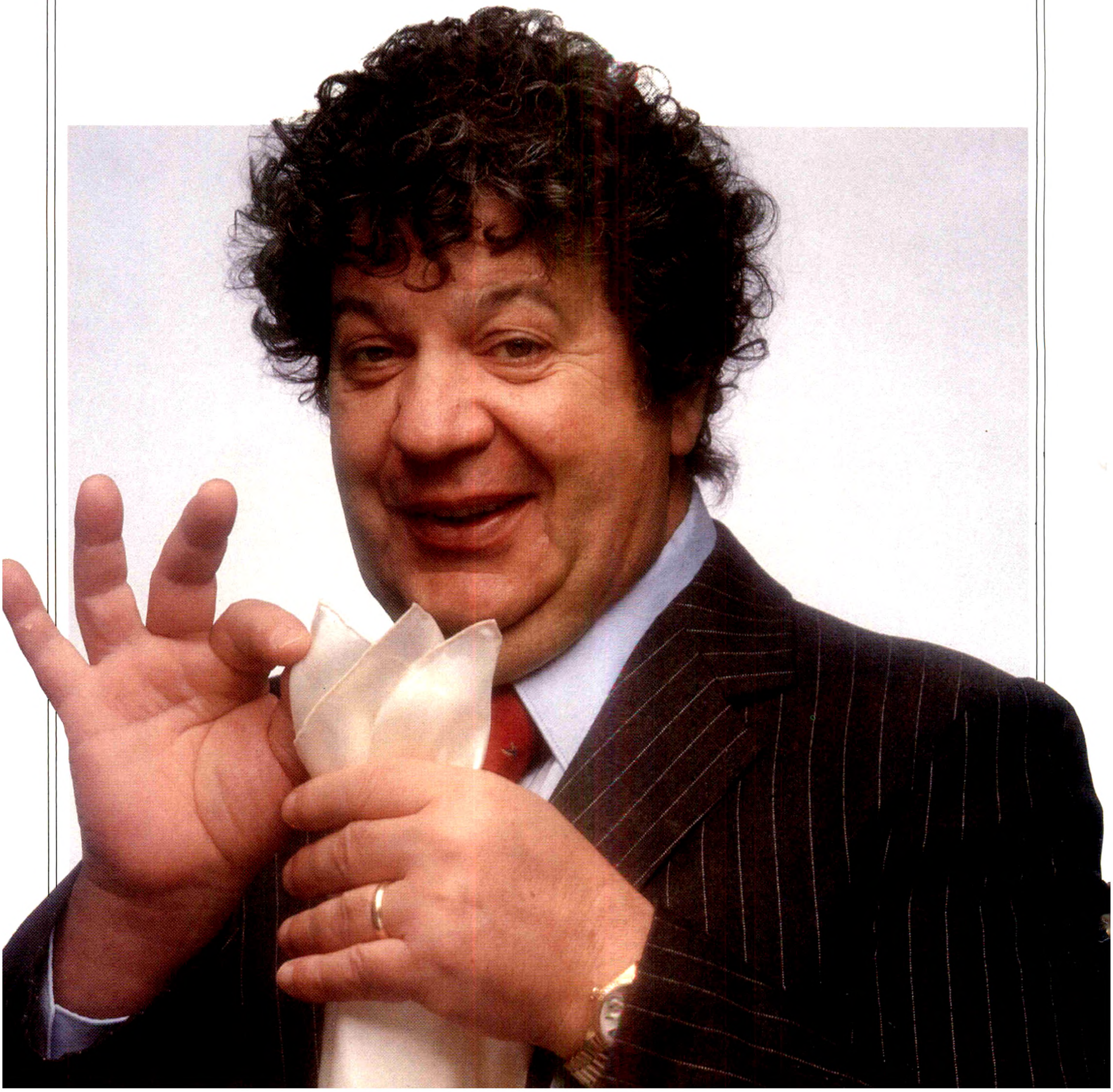

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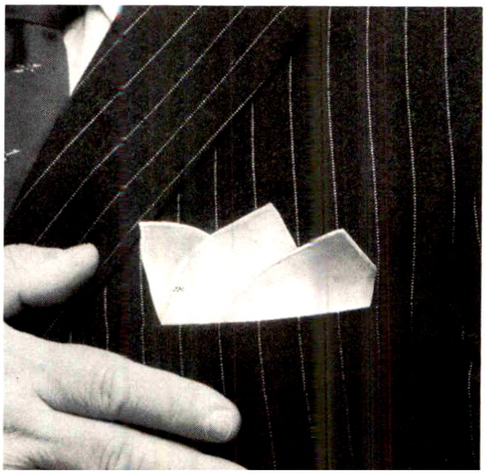

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EYE MOVEMENTS IN CEREBELLAR AND COMBINED CEREBELLOBRAINSTEM DISEASES

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We report a quantitative analysis of eye movement disturbances in patients with isolated cerebellar disorders and patients with cerebellar disorders and concomitant brainstem involvement. The most characteristic abnormalities in the exclusively cerebellar patients were increased velocities of the slow phases of vestibular nystagmus induced by rotation in the dark and increased peak velocities of the fast phases of optokinetic nystagmus induced by full-field optokinetic stimuli. Dysmetria of saccades was found in three of six cerebellar patients and gaze nystagmus in all six patients. The typical findings in the combined cerebellobrainstem group were reduced peak velocities of voluntary saccades, defective smooth pursuit and reduced peak velocities of the fast component of nystagmus during rotation in both the dark and light. All patients with combined cerebellobrainstem disorder had dysmetric voluntary saccades and gaze nystagmus. The numbers of superimposed saccades during smooth pursuit were uniformly increased. Release of inhibition in cerebellar disorders may explain the hyperresponsiveness and inaccuracy of eye movements found in this study. In addition, when lesions also involve the brainstem, however, integrative centers coding eye velocity are affected, leading to slow and inaccurate eye movements. These features elicited clinically may be useful in the diagnosis of cerebellar and brainstem disorders.

INTRODUCTION

Previous studies in patients with presumed cerebellar lesions have often failed to describe a consistent pattern of oculomotor abnormalities.[1,2] This inconsistency may have been due to the presence of lesions also involving the brainstem in some of the patients. Recently eye movement disorders in patients with presumed cerebellar atrophy have been reported.[3,4] It was not documented, however, whether the findings were similar in cerebellar disorders irrespective of etiology. Furthermore, except for voluntary saccades, no analysis of fast eye movements was made. As will be demonstrated in the present results, differences in fast phases of nystagmus can be just as indicative of a cerebellar lesion as those in slow phases of nystagmus.

In this study, we analyzed the patterns of the various types of eye movements in two groups of patients: the first with signs of cerebellar origin only, and the second with signs of both cerebellar and brainstem involvement. First, we hoped to distinguish these two groups of patients on the basis of characteristic differences in the oculomotor function and second, we wanted to compare the vulnerability of different types of rapid eye movements.

METHODS

Each group consisted of six patients (Table 1). The first group had exclusive signs of cerebellar involvement, while the other group exhibited cerebellar dysfunction combined with disorders of the cranial nerves and of sensory or pyramidal tracts, indicating involvement of brainstem structures (Table 2). The diagnosis was confirmed by neurological work-up including neuro-ophthalmological examination and computerized axial tomography.

As controls, we used 20 normal persons without any history of vestibular or neurological disease, ten males and ten females. The mean age was 48 years (range 23 to 72). The age of the controls corresponded roughly to those of the diseased subjects (Table 1).

Test Procedure. Voluntary saccades were evoked by asking the patient to look alternatingly at light diodes located horizontally 0.08, 0.17, 0.35 and 0.59 radians on each side of the midline. At least five saccades were recorded for each angle and direction.

Smooth pursuit was evoked by telling the patient to track a light spot 30 mm in diameter, at a distance of 160 cm, moving at a constant velocity on a horizontal screen. The test was conducted at velocities of 0.17, 0.35, 0.52, 0.70, 0.87 and 1.05 radians per second (rps). The test was performed both to the right and to the left. Five recordings were made in each direction and at each velocity.

TABLE 1. DIAGNOSIS AND DURATION OF SYMPTOMS IN PATIENTS WITH CEREBELLAR AND CEREBELLOBRAINSTEM DISORDERS

Patients				*Duration of Symptoms Before EOG*
Group	*No.*	*Age*	*Diagnosis*	*Recording*
Cerebellar disorders	1	49	Infarction	2 wk
	2	39	Atrophy	1½ yr
	3	52	Atrophy	1 yr
	4	50	Metastasis	1½ mo
	5	53	Multiple sclerosis	2 mo
	6	52	Hematoma	1½wk
Cerebellobrainstem disorders	7	33	Degeneration	1 yr
	8	47	Encephalitis	1 yr
	9	27	Medulloblastoma	11 yr
	10	36	Infarction	2 wk
	11	69	Metastasis	1 yr
	12	33	Ependymoma	2 yr

EOG - Electro-oculogram.

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TABLE 2. EVIDENCE OF INVOLVEMENT OF DIFFERENT STRUCTURES IN PATIENTS WITH CEREBELLAR AND CEREBELLOBRAINSTEM DISORDERS

Patients Group	*No.*	*Cranial Nerves* *I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*	*XII*	*Pyramidal Tracts*	*Cerebellum*
Cerebellar disorders	1														+
	2														+
	3														+
	4														+
	5														+
	6														+
Cerebellobrainstem disorders	7													+	+
	8			+		+	+	+	+					+	+
	9									+	+				+
	10					+									+
	11												+		+
	12									+					+

Vestibular nystagmus was induced by rotating the subject in a chair accelerated within one second to a constant velocity of 2.1 rps. After rotation for one minute the chair was decelerated to a standstill within one second. The rotatory and postrotatory responses were measured.

Optokinetic nystagmus was induced by rotating, around the patient, a striped cylinder at a velocity of 1.6 rps.

Optovestibular nystagmus was evoked by rotating the patient, with eyes open, in the same way as in the rotation test but this time inside the striped cylinder.

Each patient was examined for *spontaneous* and *gaze nystagmus*, with eyes open in darkness during the electro-oculographic recordings and with Frenzel's glasses in light.

The eye movements were recorded with a DC electro-oculographic technique with infinite time constant and upper cutoff frequency of 15 Hz. Horizontal eye movements were recorded bitemporally, and vertical eye movements were recorded monocularly. Standard electrodes (Medicotest) with jelly were used. The recorder was a DC-coupled ink-jet writer (Mingograph M 81, Siemens Elema, Stockholm). Paper speed was 100 mm/s. Two calibration tests were made, one before and one in the middle of the test.

The main thrust of this study was to analyze velocities of voluntary saccades, smooth pursuit and velocities of the fast and slow components of vestibular, optokinetic and optovestibular nystagmus. In addition, the accuracy of the saccades and the total number of superimposed saccades during smooth pursuit were measured.

Calculation and Statistical Evaluation. Peak velocity was measured from the recordings by handscoring and the data were calculated by computer (Univac-11-08-EXC-8). As the velocity of rapid eye movements is related to the amplitude, the peak velocities of the rapid eye movements were arranged in six different groups according to amplitude.[5,6] Maximum velocity of the slow component was measured at the response culmination. The maximum velocity of the smooth pursuit was measured during the time the patient was observing the target (the velocity of the superimposed saccades was not studied). The peak velocity of each type of eye movement for each patient was compared to the mean of the peak velocities in 20 normal subjects. Those velocities which fell outside the 95% confidence limit were regarded as pathological. The accuracy of the initial saccade, expressed by the amplitude, was compared to the mean value in 20 normal subjects at amplitudes of 0.35 and 1.05 radians. Values outside 2 SD from the mean value were regarded as pathological. The same evaluation was made for the total number of superimposed saccades during a constant period of eye tracking.

RESULTS

Voluntary Saccades. The results obtained by analyzing the peak velocities of voluntary saccades are shown in Figure 1. In the cerebellar disorder group, reduced peak velocities were observed in one, normal peak velocities in four, and increased peak velocities in one patient. In the cerebellobrainstem dis-

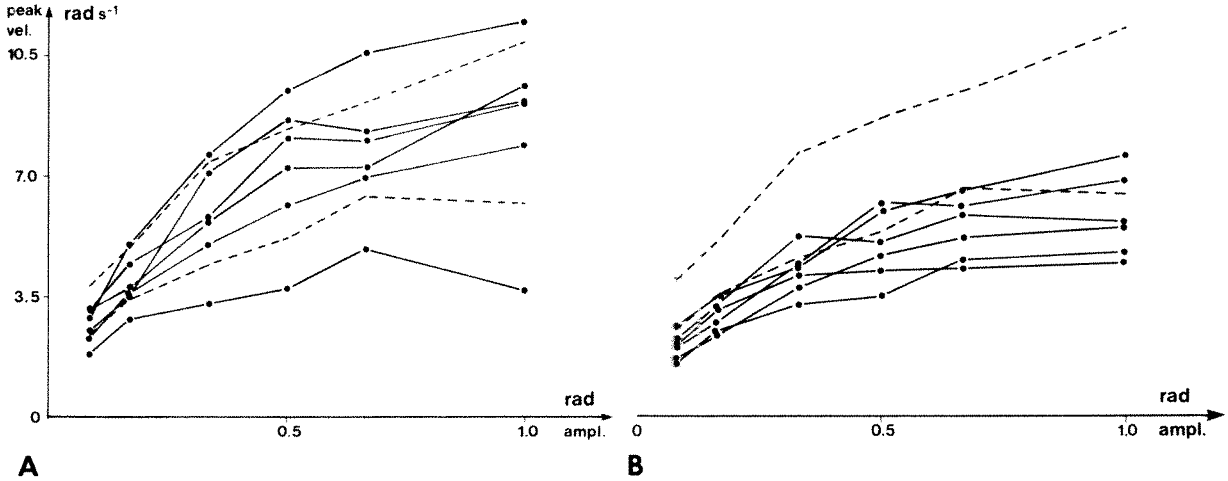

Fig. 1. Amplitude-peak velocity relationship of voluntary saccades in patients with A) cerebellar and B) cerebellobrainstem disorders. Each curve represents one individual. Dashed lines represent 2 SD on each side of mean peak values in 20 normal subjects.[5] Vel. - Velocity; ampl. - Amplitude; rads[1] - Radians per second.

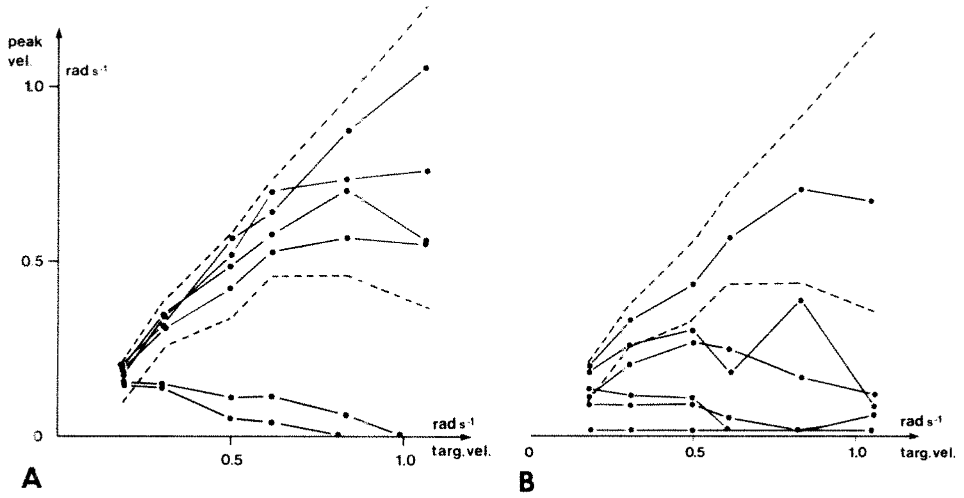

Fig. 2. Maximum velocities of smooth pursuit at different target velocities in six patients with A) cerebellar and B) cerebellobrainstem disorders. Dashed lines and abbreviations as in Fig. 1. Targ. vel. - Target velocity.

order group all patients displayed reduced peak velocities.

Inaccurate voluntary saccades, primarily hypometria, were found in three cerebellar patients. All six patients with cerebellobrainstem disorders showed dysmetric voluntary saccades.

Smooth Pursuit. Figure 2 exhibits individual maximum smooth pursuit velocity curves. In the cerebellar disorder group, smooth pursuit velocity was reduced in two and normal in four patients, while in the cerebellobrainstem disorder group, five subjects exhibited reduced smooth pursuit velocities and the velocity was normal in one.

The number of superimposed saccades was increased in two subjects in the cerebellar group. One of them had normal smooth pursuit velocity, while the second had significantly reduced velocity. The frequency of superimposed saccades in the cerebellobrainstem group was increased in five and normal in one patient.

Vestibular Responses. Eye movements in response to rotational stimuli revealed pronounced differences between the two groups. In the cerebellar disorder group, the maximum velocity of slow phases of nystagmus was increased in five subjects and decreased in one, whereas in the cerebellobrainstem disorder group two subjects exhibited reduced velocity in the slow component of nystagmus and four were normal (Fig. 3).

The peak velocity of fast phases of nystagmus in cerebellar patients (Fig. 4A) was significantly increased in three, within the normal range in two and significantly slow in one subject. However, in the cerebellobrainstem group, five patients presented abnormally slow peak velocities, while the velocity was increased in one patient (Fig. 4B).

Optokinetic Responses. In patients with cerebellar disorders, the slow component of optokinetic nystagmus was above the normal range in two, within normal limits in three, and below the normal range in one subject. In the patients with cerebellobrainstem disorders, the maximum velocity of the slow component of optokinetic nystagmus was normal in one and decreased in five subjects.

In the fast components of optokinetic nystagmus the peak velocities in cerebellar patients were increased in five subjects and normal in one, while in the cerebellobrainstem patients, the peak velocities of the fast component were normal in two and decreased in four.

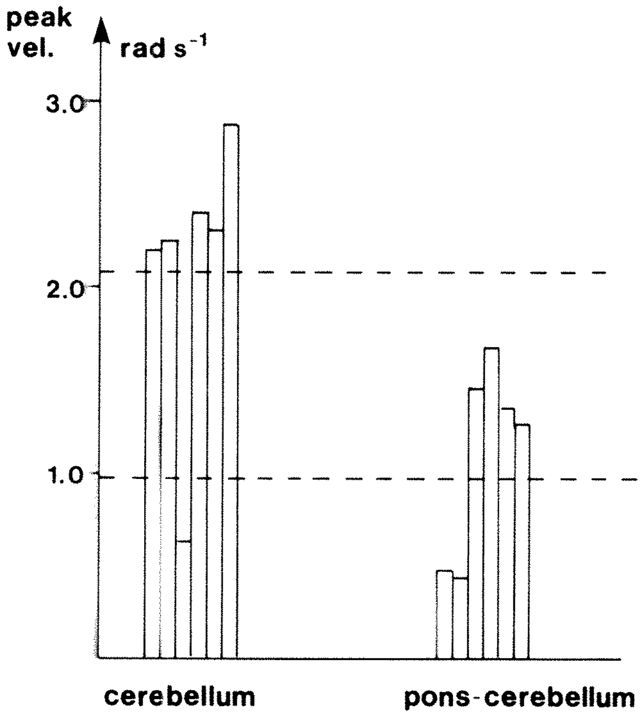

Fig. 3. Slow phase velocities at the culmination response of the postrotatory reaction in patients with cerebellar and cerebellobrainstem disorders. Dashed lines and abbreviations as in Fig. 1.

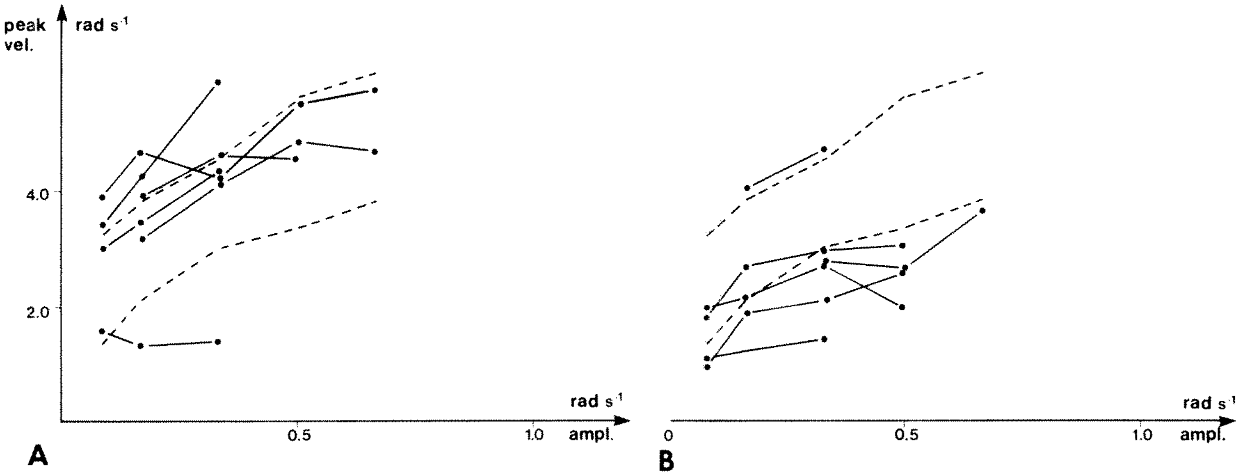

Fig. 4. Amplitude-peak velocity relationship of the fast phases in the rotatory test in A) cerebellar and B) cerebellobrainstem patients. Dashed lines and abbreviations as in Fig. 1.

Optovestibular Responses. All cerebellar patients who were tested (5/6) had normal peak velocities in the slow phases (Fig. 5). In the fast phases, three patients exhibited significantly increased velocities. In the cerebellobrainstem group, three patients had decreased velocities in both components, while two had decreased velocities only in the fast phase.

Table 3 is a summary of the findings in all types of eye movements.

Spontaneous and Gaze Nystagmus. In the cerebellar disorder group, two of the patients exhibited a horizontal spontaneous nystagmus, five had direction-changing gaze nystagmus, and one had direction-fixed gaze nystagmus. Downbeat nystagmus was observed in one patient.

In the cerebellobrainstem group, three subjects exhibited spontaneous nystagmus and all subjects demonstrated direction-changing gaze nystagmus.

DISCUSSION

The vestibulocerebellum and the dorsal and posterior vermis are particularly closely related to ocular motility.[7-10] These areas are known to receive afferent signals via visual and vestibular pathways.[11] Lesions of the dorsal vermis can cause saccadic instability,[12] while changes in smooth pursuit are found in cases of floccular process.[13,14]

Findings of increased velocities of the two types of rapid eye movement, voluntary saccades and fast phases of nystagmus (Table 3), have not previously been reported in cerebellar lesions. Thus, in such cases, a normal amplitude-velocity relationship of voluntary saccades has been reported by Aschoff and Cohen,[7] Zee et al,[4] and by Ellenberger et al,[15] while even reduced velocities were found by Baloh et al.[3] The conclusions drawn from our findings are supported to some extent by the observation of Ron and Robinson[16] who, by varying electrical stimulation of the cerebellum, were able to provoke variations in saccadic velocity. It is not clear, however, how this velocity increase, as found in our study, can be explained. It may well indicate an increased frequency of spikes in neurons responsible for rapid eye movements, or a too-early interruption of a saccade or quick phase preprogrammed to larger amplitudes. Some observations in animal experiments suggest the latter possibility.[16]

Inaccuracy of voluntary saccades is a phenomenon repeatedly found in patients with lesions of the cerebellum.[4,17] Both hypermetria and hypometria occur, even if hypometria is the more common[18] and is rather typical of vermal lesions.[7,12] Hypometria of saccades is a common finding in various

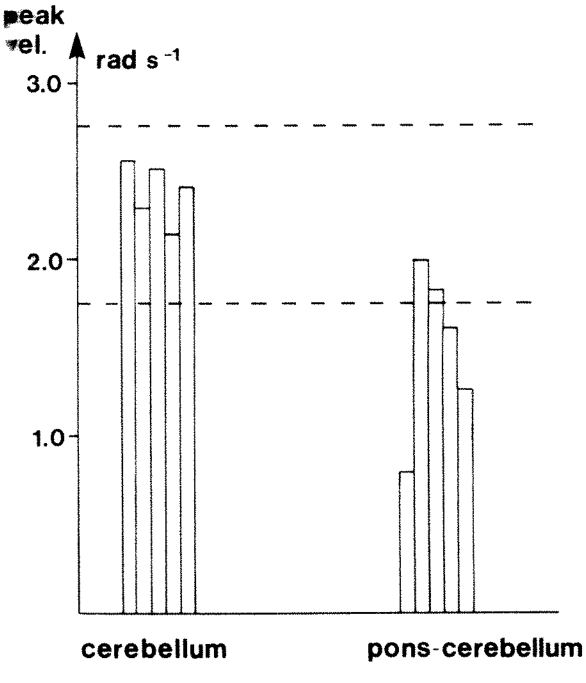

Fig. 5. Maximum slow phase velocities in the optovestibular test in patients with cerebellar and cerebellobrainstem disorders. Dashed lines and abbreviations as in Fig. 1.

TABLE 3. FINDINGS* OF EYE-MOVEMENT TESTS IN PATIENTS WITH CEREBELLAR AND CEREBELLOBRAINSTEM DISORDERS

Patients Group	*No.*	*Type of Lesion*	*Pursuit Velocity*	*Saccade Velocity*	*Rotation*		*OKN*		*Optovest.*		*Dysmetria*	*Superimposed Saccades*
					Fast	*Slow*	*Fast*	*Slow*	*Fast*	*Slow*		
Cerebellar disorders	1	Infarction	N	N	+	+	+	+	N	N	No	N
	2	Atrophy	N	+	+	+	+	+	+	N	No	N
	3	Atrophy	—	N	N	+	+	—	+	N	Yes	+
	4	Metastasis	N	N	+	+	+	N	+	N	Yes	N
	5	Multiple sclerosis	N	N	N	+	+	N	N	N	No	+
	6	Hematoma	—	—	—	—	N	N			Yes	N
Cerebellobrainstem disorders	7	Degeneration	N	—	—	—	—	—	—	—	Yes	N
	8	Encephalitis	—	—	+	—	N	—			Yes	+
	9	Medulloblastoma	—	—	—	N	—	—	—	N	Yes	+
	10	Infarction	—	—	—	N	N	N	—	N	Yes	+
	11	Metastasis	—	—	—	N	—	—	—	—	Yes	+
	12	Ependymoma	—	—	—	N	—	—	—	—	Yes	+

*Values outside 2 SD from the mean values in 20 normal subjects are regarded as pathological.

N - Normal; — - Decreased; + - Increased; OKN - Optokinetic nystagmus; Optovest - Optovestibular.

brain disorders and a very striking inaccuracy of saccades has been found in patients with frontal lobe lesions.[19] In the present study inaccuracy of saccades, reflected overwhelmingly by hypometria, was more frequently found in patients with cerebellobrainstem lesions than in patients with cerebellar lesions.

The velocity of smooth pursuit was decreased in two of six patients with cerebellar disorders. Baloh et al[3] and Zee et al[4] frequently found impaired smooth pursuit in patients with cerebellar ataxia. The visual information for smooth pursuit is believed to be projected via the dorsal capsule of the inferior olive to the vestibulocerebellum.[20,21] Furthermore, selective lesions of the flocculus in the monkey impair the ability for smooth tracking.[14] In hereditary cerebellar ataxia, cell degeneration occurs in the flocculus, the inferior olive and various cerebellar nuclei,[4] all structures possibly important for performing smooth pursuit. In the present study, some cerebellar patients had normal smooth pursuit velocity, indicating that the floccular output was still adequate in these cases. Another possibility might be that the cerebellar dysfunction was compensated for by mechanisms elsewhere.[4] In contrast to this normal smooth pursuit, five of six patients with cerebellobrainstem lesions showed a reduced smooth pursuit velocity. It must therefore be expected that in the brainstem, structures involved in performing smooth pursuit are very sensitive to lesions, as was also indicated in a previous study.[22]

Low velocity in smooth pursuit affected by cerebellobrainstem lesions was compensated for by superimposed saccades. In one of the patients with a cerebellar disorder we found normal smooth pursuit velocity, and in spite of this an increased number of superimposed saccades. Thus, a higher readiness for saccadic release was present than was needed in order to assist the smooth pursuit system. However, in the majority of the patients with cerebellar disorders, superimposed saccades compensated for a low smooth pursuit gain.

The inhibitory effect of the cerebellum as exerted on the vestibular nuclei[23] provides an explanation for the changes in the velocity of the nystagmic slow component. Moreover, Ito et al[24] showed that electrical stimulation of the flocculus causes increased inhibition of the ipsilateral vestibular nucleus and hence a diminished horizontal canal reflex. Furthermore, Takemori and Suzuki[25] observed that lesions of the deep cerebellar nuclei, responsible for relaying the major output from the cerebellar cortex, lead to a marked increase in the velocity and duration of caloric nystagmus. In cerebellar lesions, loss of inhibition of the neuronal activity initiated by the horizontal canal system[23] could thus explain the present findings of vestibular hyperactivity in patients with cerebellar disorders.

Several reports have dealt with optokinetic nystagmus in experimental cerebellar lesions. In foveate animals the optokinetic slow phase consists of two portions.[26,27] The initial rise, characterized by an immediate increase in velocity of the optokinetic nystagmus, is followed by a slow rise, consisting of accumulations of velocity increments.[27] The former is believed to use smooth pursuit mechanisms and the latter, vestibular mechanisms.[28,29] In nonfoveate animals, like rabbits,[30] ablation of the cerebellum has little effect on the slow phase velocity of optokinetic nystagmus, indicating that optokinetic engagement via vestibular pathways is not dependent on the cerebellum. In foveate mammals, as in monkeys[14] or in human beings,[31] cerebellar lesions lead to a decrease in slow phase velocity, its time constant being prolonged together with a reduced gain. This indicates that optokinetic nystagmus using smooth pursuit mechanisms is dependent on cerebellar function.

When in the optokinetic test the optokinetic drum is operated at higher velocities (1.57 rps), the patient is quite unable to fixate.[32] Therefore, it is mainly the reflexive type of optokinetic nystagmus which is tested.[33] This can explain why the optokinetic responses could remain intact in cerebellar lesions and even be enhanced in much the same way as the slow component of vestibular nystagmus.

The velocity of the slow component of optovestibular nystagmus was normal in all the subjects with cerebellar disorders, while it was decreased in all but two subjects with cerebellobrainstem lesions. The reason for the normal values could be 1) cooperation between the visual and the vestibular systems compensating for defects in optokinetic and vestibular nystagmus, or 2) hyperactivity in the vestibular response, restoring the reduced optokinetic response.

CONCLUSIONS

In spite of the diversity of the results in the different tests, they are connected by a thread of consistency that seems to suggest a constellation that is unique to a cerebellar disorder compared with a cerebellobrainstem disorder.

It seems possible to distinguish a cerebellar lesion from one that involves the brainstem on the basis that "pure" cerebellar patients generally show 1) increased or normal peak velocities of voluntary saccades, while the cerebellobrainstem patients have decreased velocities; 2) increased or normal responses of the maximum velocity in the fast and/or slow component of vestibular nystagmus, compared with decreased or normal velocities in cerebellobrainstem patients; 3) increased or normal peak velocities in the fast component in optokinetic nystagmus, whereas decreased or normal velocities in the same type of nystagmus are found in cerebellobrainstem patients; 4) increased or normal peak velocities in the fast phase of the optovestibular test compared with decreased velocities in the cerebellobrainstem group.

In the same way it would seem possible to distinguish a patient with a cerebellar lesion from a normal person on the following basis: 1) inaccuracy of voluntary saccades, 2) defective smooth pursuit, 3) increased peak velocities in the fast and/or slow component in the rotatory test, 4) increased peak velocities in the fast component of optokinetic nystagmus, and 5) inability to hold eccentric gaze.

REFERENCES

1. Dow RS, Moruzzi G. The physiology and pathology of the cerebellum. Minneapolis: University of Minnesota Press, 1958.

2. Potthoff PC, Haustein M. Nystagmus and Elektronystagmogramm nach Kleinhirntumoroperationen. Neurochirurgia (Stuttg) 1974; 13:174-88.

3. Baloh RW, Konrad HR, Honrubia V. Vestibulo-ocular function in patients with cerebellar atrophy. Neurology (Minneapolis) 1975; 25:160-8.

4. Zee DS, Yee DR, Cogan DC, Robinson DA, Engel WK. Ocular motor abnormalities in hereditary cerebellar ataxia. Brain 1976; 99:207-34.

5. Henriksson NG, Pyykkö I, Schalén L, Wennmo C. Velocity patterns of rapid eye movements. Acta Otolaryngol (Stockh) 1980; 89:504-12.

6. Schalèn L. Quantification of tracking eye movements in normal subjects. Acta Otolaryngol (Stockh) 1980; 90:404-13.

7. Aschoff JC, Cohen B. Changes in saccadic eye movements produced by cerebellar cortical lesions. Exp Neurol 1971; 32: 123-33.

8. Ito M. The vestibulo-cerebellar relationships: vestibulo-ocular reflex arc and flocculus. In: Naunton RF, ed. The vestibular system. New York: Academic Press, 1975:129-46.

9. Llinás R, Wolfe JW. Functional linkage between the electrical activity in the vermal cerebellar cortex and saccadic eye movements. Exp Brain Res 1977; 29:1-14.

10. Precht W. Neuronal operations in the vestibular system. Berlin: Springer-Verlag, 1978.

11. Berthoz A, Llinás R. Afferent neck projection to the cat cerebellar cortex. Exp Brain Res 1974; 20:385-401.

12. Ritchie L. Effects of cerebellar lesions on saccadic eye movements. J Neurophysiol 1976; 39:1246-56.

13. Miles FA, Fuller JH. Visual tracking and the primate flocculus. Science 1975; 189:1000-2.

14. Zee DS, Yamazaki A, Gucer G. Ocular motor abnormalities in trained monkeys with floccular lesions. Soc Neurosci Abstr 1978; 4:168.

15. Ellenberger C, Keltner JL. Stroud MH. Ocular dyskinesia in cerebellar disease. Brain 1972; 95:685-92.

16. Ron S, Robinson DA. Eye movements evoked by cerebellar stimulation in the alert monkey. J Neurophysiol 1973; 36: 1004-22.

17. Baloh RW, Honrubia V, Sills A. Eye-tracking and optokinetic nystagmus. Ann Otol Rhinol Laryngol 1977; 86:108-14.

18. Zee DS. Disorders of eye-head coordination. In: Brooks BA, Bajandas FJ, eds. Eye movements. New York: Plenum Press. 1977:9-39.

19. Dahlen AI, Fex S, Henriksson NG, Pyykkö I, Wennmo C. Dyspraxia of speech and of eye motility. Acta Otolaryngol (Stockh) 1980; 89:144-51.

20. Simpson JI, Soodak RE, Hess R. The accessory optic system and its relation to the vestibulocerebellum. In: Granit R, Pompeiano O, eds. Reflex control of posture and movement. Progress in Brain Research, Vol 50. Amsterdam: Elsevier North Holland Biomedical Press, 1979:715-24.

21. Barmack NH, Hess DT. Multiple-unit activity evoked in dorsal cap of inferior olive of the rabbit by visual stimulation. J Neurophysiol 1980; 43:151-64.

22. Wennmo C. Hindfelt B. Eye movements in brainstem lesions. Acta Otolaryngol (Stockh) 1980; 90:230-6.

23. Angaut P, Brodal A. The projection of the "vestibulo-cerebellum" onto the vestibular nuclei in the cat. Arch Ital Biol 1967; 105:441-79.

24. Ito M, Nisimaru N, Yamamoto M. Specific patterns of neuronal connexions involved in the control of the rabbit's vestibulo-ocular reflexes by the cerebellar flocculus. J Physiol (Lond) 1977; 265:833-54.

25. Takemori S, Suzuki JI. Cerebellar control of the vestibulo-oculomotor reflex. In: Hood JD, ed. Vestibular mechanisms in health and disease. London: Academic Press, 1978:99-106.

26. Cohen B, Matsuo V, Raphan TH. Quantitative analysis of the velocity characteristics of optokinetic nystagmus and optokinetic afternystagmus. J Physiol (Lond) 1977; 270:321-44.

27. Raphan TH, Matsuo V, Cohen B. Velocity storage in the vestibulo-ocular reflex arc (VOR). Exp Brain Res 1979; 35:229-48.

28. Kubo T, Matsunaga T, Igarashi M. Vestibular unitary responses to visual stimulation in the rabbit. Acta Otolaryngol (Stockh) 1979; 88:117-21.

29. Keller EL, Precht W. Persistence of visual response in vestibular nucleus neurons in cerebellectomized cat. Exp Brain Res 1978; 32:591-4.

30. Collewijn H. Dysmetria of fast phase of optokinetic nystagmus in cerebellectomized rabbits. Exp Neurol 1970; 28:144-54.

31. Baloh RW, Jenkins HA, Honrubia V, Yee RD, Lau CG. Visual-vestibular interaction and cerebellar atrophy. Neurology (Minneapolis) 1979; 29;116-9.

32. Holm-Jensen S, Peitersen E. Optokinetic nystagmus in normal human subjects. In: Hood JD, ed. Vestibular mechanisms in health and disease. London: Academic Press, 1978:280-7.

33. Honrubia V, Downey WL, Mitchell BA, Ward PH. Experimental studies on optokinetic nystagmus. II. Normal humans. Acta Otolaryngol (Stockh) 1968; 65:441-8.

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FIFTH INTERNATIONAL SYMPOSIUM ON THE FACIAL NERVE

The Fifth International Symposium on the Facial Nerve will be held in Bordeaux, France, on September 3-6, 1984. Topics to be covered include basic sciences, clinical and paraclinical investigations, hemifacial spasm, medical and physical care, neurosurgery of the facial nerve, anastomosis surgery and plastic surgery. Presentation will be in English/French (with simultaneous translation).

Papers are being solicited and may not exceed ten minutes in length for presentation. Titles should be forwarded to the Congress Secretariat, Fondation Portmann, 114 Avenue d'Ares, 33074 Bordeaux Cedex, France, before June 1983.

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THE DEAFNESS RESEARCH FOUNDATION — 1984 RESEARCH GRANTS

The Deafness Research Foundation invites applications for its 1984 grants in support of new research that promises to advance understanding of the causes, treatment and prevention of deafness and related ear disorders. The grants will be awarded to tax-exempt institutions for projects that will begin January 1, 1984, with the principal investigator of each project a member of the staff or faculty of such institution. The grants do not exceed $10,000, and can be competitively renewed with the same limit for an additional one or two years. Applications are reviewed for their scientific merit and for their direct or potential clinical importance.

The deadline for first-year applications is July 15, 1983; for renewal applications, August 15, 1983. For full information on the grants program, and for the required application form, please write to Grants Administrator, Deafness Research Foundation, 55 East 34th Street, New York, NY 10016.

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EPIDEMIOLOGY OF SECRETORY OTITIS MEDIA

A DESCRIPTIVE COHORT STUDY

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To determine the prevalence, incidence, and course of secretory otitis media in an age-group population, 404 3-year-old children in a town in Denmark were examined at 6-, 8-, and 12-week intervals over a 6-month period. At each of the four examinations approximately 20% of the children had middle ear effusion (MEE); it was found at least once in 42% of the children, and 6% had persistent effusion at all four examinations. Average duration of MEE was 3 months. Since spontaneous recovery rarely occurred when MEE had been present for more than 3 months, active intervention is recommended after the condition has been followed for this length of time. The highly fluctuating course of MEE demonstrated in early childhood has important implications for concepts in pediatric middle ear disease and treatment.

INTRODUCTION

Secretory otitis media (SOM) is a disease in which there is a middle ear effusion (MEE), the tympanic membrane is intact (nonperforated), and symptoms of acute inflammation are absent. Because MEE impedes sound transmission, it results in an average conductive hearing loss of 22 to 33 dB in 3-year-old children.[1] Hearing loss at this age can have a deleterious effect on language and speech development.[2] Moreover, evidence indicates that permanent middle ear disorders may result from conditions which first develop at an early age.[3]

Although morbidity from middle ear disorders in the first years of life is known to be great,[4-7] the incidence and prevalence of MEE in large age-group populations has apparently not been reported nor the course of SOM in such groups systematically documented. This study was undertaken to determine the prevalence, duration, and course of MEE in 3-year-old children in a medium-size city in Denmark. A further objective was better understanding of the etiology and epidemiology of MEE to enhance management of this disorder and to inform decisions regarding preschool screening procedures and follow-up evaluations.

SUBJECTS AND METHODS

In 1978-1979, the population of 3-year-old (36 to 48 months) children in Hjoerring, Denmark, were screened for inclusion in the study. Selection procedures are described in detail in previous publications.[4,5,8] Of the 456 children screened, 404 were included in the study and underwent impedance audiometry testing and pneumatic otoscopy four times during the study period: August 1978, September 1978, November 1978, and February 1979. In all children intervals between testing differed by no more than ± eight days (Fig 1), and no disorder identified was treated until after the fourth testing session.

The impedance data included automatic X-Y recorded tympanometry (Madsen tympanometer, model Z0-73, testing tone 220 Hz, pressure reduction 30 mm H_2O/s, Madsen Electronics, Oakville, Ontario, Canada; Hewlett-Packard X-Y plotter, model 7010A/132 Hewlett-Packard Co, Avondale, Pa) combined with contralateral and ipsilateral measurement of middle ear reflexes at 1,000 Hz with no pressure gradient across the tympanic membrane. If no discernible deflection of the written reflex recordings was noted at 100 dB (ruling out artifacts and not considering on/off phenomena), the middle ear reflexes were considered to be absent.

Geographical Context. The municipality of Hjoerring consists of a medium-size urban town with a population of approximately 20,000, several villages, and fairly widespread, sparsely built-up areas. It is representative of Denmark with respect to degree of urbanization, population characteristics, and climate and geography. Denmark is in the northern temperate zone in close proximity to major seas which moderate its climate. Temperature and rainfall during the study period were comparable to mean values reported during the same months over a period of years. The study period was also typical with respect to incidence of contagious disease.

Classification of Results. As pointed out by Haughton,[9] detection of fluid via tympanometry is a relatively difficult task in an ENT clinic population because often dry ears have conductive defects that produce an abnormally low compliance at the drum. Brooks[10] reported that the frequency of abnormal tympanometry not related to the presence of MEE increased with age. Impedance audiometry was selected because it is an objective, reliable, and noninvasive method of demonstrating middle ear disturbance and is practical for use with all ages.[8] Since the validity of the impedance test for predicting MEE in preschool children has not been established, obtaining a measure of validity was a further objective of the study (Fig 1).

In 44 children the tympanogram remained flat or showed an intratympanic pressure ≤ -100 mm H_2O persistently in one or both ears at all four examinations. These children had bilateral myringotomies an average of ten days (range five-15 days) after the fourth screening in February 1979. Within a half hour prior to surgery, which was carried out under general anesthesia without nitrous oxide, the impedance tests were repeated and the results compared with the myringotomy findings (Table 1). The experienced ENT surgeon who performed the operations and recorded the myringotomy findings did not know the preceding impedance results. Of the 88 operated ears, 46 (52%) contained fluid (Table 1). As will be seen and as demonstrated in another cohort of 3-year-olds,[8] a flat tympanogram almost guaranteed a

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From the ENT Department, Hjoerring Hospital, Denmark. The study was supported by the Danish Medical Research Council grants 512- 10525, 512-15724, and 552-911, by the Danish Foundation for the Advancement of Medical Science, grant 27/78; by the Niels Jensen Memorial Foundation; and by the Medical Research Foundation for Northern Jutland, grant 2-16-30.

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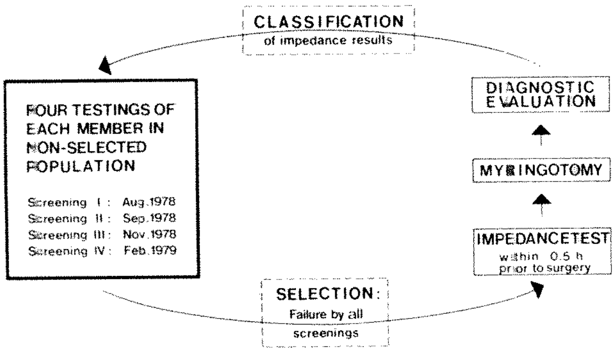

Fig 1. Plan of study.

finding of fluid in the middle ear. But the reverse conclusion was not supported with eight ears exhibiting effusion without having a flat tympanogram. In six of these ears, however, the middle ear reflexes were absent (Table 1). By specifying a flat curve or a middle ear pressure ≤ – 100 mm H_2O combined with absent middle ear reflexes, it was possible on the basis of impedance audiometry to classify 97% of the material correctly as middle ears which contained effusion and those which did not. Thus, the accuracy of the impedance test reported by others[11] was verified and its validity for preschool ages established. In this study, criterion 4 (Table 1) was used as the sole diagnostic indicator and all ears were classified on this basis as having or not having MEE. Otoscopy data were not included in the analysis since they could not enhance diagnostic accuracy, but could interfere with the objectivity of the case-finding method.

RESULTS

Ten children were excluded from the analysis when first seen (Table 2): six with grommets in situ, one with a defect of the tensa, one with an undetected cholesteatoma, and two for whom arrangements had been made prior to the study period to have grommets inserted. Although 25 children dropped out during the study period, this attrition could not influence the results (Table 2). Of the total population of 456 3-year-olds in the region, 404 (88.6%) were tested at all four times and this group comprised the present study series. No child in the series had adenoidectomy, myringotomy tubes, or paracentesis during the study period.

Prevalence. Seventeen percent to 20% of the subjects (13 to 16% of ears) had MEE at each screening (Table 3). The mild increase in February was not significant (Cochran's Q test, $p > 0.05$). Although prevalence of MEE was relatively stable from test to test with positive findings in approximately one of every five subjects, the group with MEE was not static; ie, to a large extent different children and ears were affected from test to test.

Incidence. Incidence of MEE (number of new cases during a specific time period) averaged 29 per interval between tests: 29 new cases in September, 24 in November, and 35 in February (Table 4). However, these data are incomplete, as noted in the Comments section. Over the 6-month study period no MEE was found in 238 (59.9%) of 404 subjects, but at least one episode occurred in 166 (41.1%). Of the 182 episodes of MEE recorded in 166 subjects, 9.6% were recurrences (Fig 2). In 89 (53.6%) subjects with effusion, MEE was present on only one of the four examinations.

Duration and Course. Of the 78 children with MEE at the first (August) examination, 28 (36%) had the condition for less than 4 weeks, another 18 (23%) recovered in 12 weeks, and seven (9%) had MEE for 12-24 weeks. After 3 months' duration, the rate of recovery decreased. During the 6-month study period 50% (39) of the 78 children with MEE at the initial examination recovered spontaneously without observed recurrences, 32% (25) had persistent MEE for the period, and 18% (14) had fluctuating MEE over the study period. The 25 with persistent MEE constituted 6.2% of the 3-year-old population.

Of the 29 new cases of MEE in September, eight (27%) of the children still had MEE in November and three (10%) still had it in February (Fig 3). One third of the new cases diagnosed in November continued to have MEE in February.

COMMENTS

Diagnosis. Impedance testing predicted MEE in 52% (46) of 88 ears comprising the subpopulation on which myringotomies were performed (Table 1), while MEE in the total population of 3-year-olds was less than one third as prevalent, ranging from 13% to 16% (Table 3). However, the predictive value of a test depends not only on diagnostic accuracy, but also on the prevalence of the disease in the population tested. For this reason the predictive value of a positive test in the 3-year-old population (404) was 0.9 using criterion 4 (Table 1) as compared with 0.7 using, eg, criterion 2. The merit of the stapedius reflex in diagnosing MEE seems to be

TABLE 1. TYMPANOMETRIC DIAGNOSIS OF MIDDLE EAR EFFUSION IN RELATION TO FINDINGS AT 88 MYRINGOTOMIES IN 3-YEAR-OLD CHILDREN (N = 44)

	Tympanometric MEE:	*Yes*		*No*		*Sensitivity*	*Specificity*	*Accuracy*
Criteria	*Myringotomic MEE:*	*Yes*	*No*	*Yes*	*No*	*(%)*	*(%)*	*(%)*
1	Middle ear pressure ≤ – 100 mm H_2O or flat curve	44	15	2	27	96	64	81
2	Middle ear pressure ≤ – 200 mm H_2O or flat curve	42	5	4	37	91	88	90
3	Flat curve	38	0	8	42	83	100	91
4	Flat curve, or pressure ≤ – 100 mm H_2O comb. with absent middle ear reflexes	44	1	2	41	96	98	97

TABLE 2. SUBJECTS IN STUDY FOLLOWED UP OR NOT SEEN FURTHER

A	*S*	*N*	*No. of Subjects** *Tested*	 *Not Further Seen*
+			82	1
0			349	10
			431	11
+	+		50	—
+	0		31	1
0	+		31	1
0	0		308	7
			420	9
+	+	+	32	—
+	+	0	18	—
+	0	+	8	1
+	0	0	22	1
0	+	+	8	—
0	+	0	22	1
0	0	+	24	—
0	0	0	277	4
			411	7

0 - Absence of MEE; + - Presence of MEE; A - August; S - September; N - November.

*456 children in complete cohort; 441 children seen.

that it enables a distinction between reduced middle ear pressures *without* MEE (reflexes present) and reduced middle ear pressures *with* MEE (no reflexes).

Epidemiology. The stability of MEE in the population over the study period (Table 3) reflects a balance between the number of new cases at each examination and the number of cases which subsided or cleared. The new cases of MEE documented at each examination, however, do not necessarily reflect incidence accurately because they do not account for MEE which may have appeared and subsided between examination dates. Similarly, possible recoveries would not be accounted for. Thus, both incidence risk (i) and recovery risk (r) contribute to the number of new and recovered cases occurring between observation times (test dates). A rough estimate of the duration of MEE is provided by the ratio of children who continued to have MEE to the number who recovered during the same time period (Table 5).

TABLE 3. PREVALENCE OF MEE IN 3-YEAR-OLD CHILDREN (N = 404)

Screening		*MEE %* *Ears*	 *Subjects*
1 —	A 1978	13.7	19.3
2 —	S 1978	13.7	19.6
3 —	N 1978	13.0	17.5
4 —	F 1979	16.0	20.5

F - February.

TABLE 4. MIDDLE EAR EFFUSION IN 404 CHILDREN AT SUCCESSIVE TEST DATES

A	*S*	*N*	*No. of Subjects*
+			78
0			326
	Total		404
+	+		50
+	0		28
0	+		29*
0	0		297
	Total		404
+	+	+	32
+	+	0	18
+	0	+	7
+	0	0	21
0	+	+	8
0	+	0	21
0	0	+	24*
0	0	0	273
	Total		404

A	*S*	*N*	*F*	*No. of Subjects*
+	+	+	+	25
+	+	+	0	7
+	+	0	+	5
+	+	0	0	13
+	0	+	+	3
+	0	+	0	4
+	0	0	+	2
+	0	0	0	19
0	+	+	+	3
0	+	+	0	5
0	+	0	+	2
0	+	0	0	19
0	0	+	+	8
0	0	+	0	16
0	0	0	+	35*
0	0	0	0	238
		Total		404

*New cases.

It is important to recognize that risk is a conditional probability referring to an individual, and that as a proportion it is dimensionless. Clearly, the 1-, 2-, and 3-month risks were almost equal (Table 5). Since we observed only prevalence of MEE at unequal intervals, absolute values for duration were not obtained. Of the 138 single cases of MEE recorded in 131 (78 + 29 + 24) children at the first three tests (Table 4), 46 episodes both set in and subsided within the observation period: 21 episodes subsided within 2 months, 20 within 3 months, and 5 within 5 months. In computing the observed maximum duration these cases were rated as having a duration of 2, 3, and 5 months, respectively. Apply-

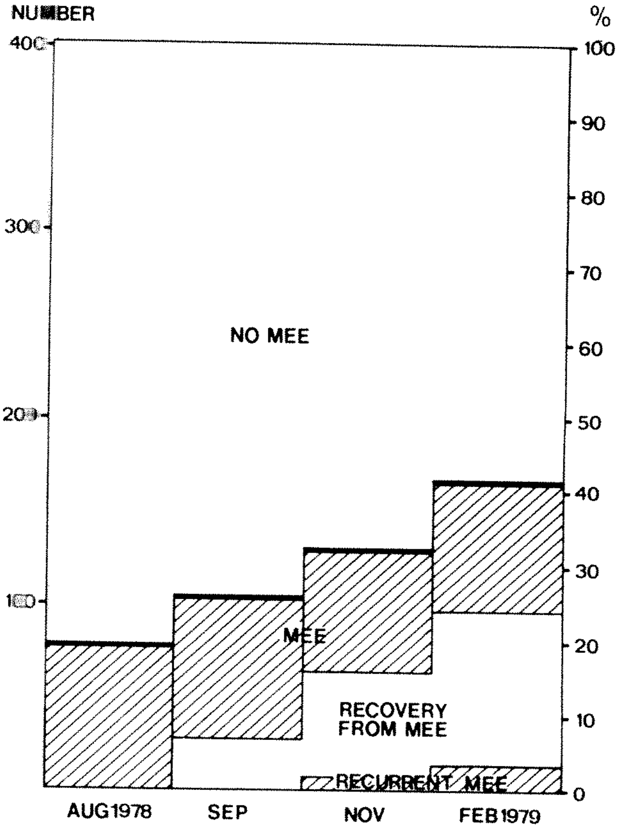

Fig 2. Six months' cumulated incidence of, recovery from, and recurrence of MEE in 404 children.

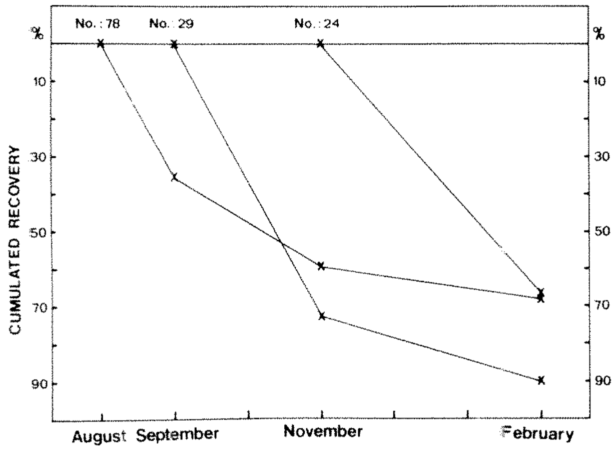

Fig 3. Cumulated rate of spontaneous recovery from MEE in 78 children diagnosed in August, in 29 children first diagnosed in September, and in 24 children first diagnosed in November 1978.

ing this principle of rating to all the cases of MEE, the observed maximum duration of 46 MEEs (with known time of onset and recovery) averaged 2.8 months; in 78 MEEs with unknown time of onset, 3.4 months; in 14 MEEs with unknown time of recovery, 3.4 months; and in all cases of MEE, average duration was 3.2 months. The 21.8% of the 3-year-olds with observed onset of MEE during the 6-month period was a minimal expression of the cumulative incidence. Incidence density, which is the ratio of the number of newly detected cases to the product: number at risk x time at risk, is a more accurate measure of morbidity. Three hundred twenty-six children were at risk for 1 month, 297 for 2 months, and 273 for 3 months, totaling 1,709 person-months. As 88 new cases developed during the 6-month period, the incidence density was 88/1,709 = 0.051/month, 0.31/half year, and 0.62/year. Counting the fraction of approximately 0.2 with MEE at the first test, total morbidity for the 6-month period would be 0.51 and for the year, 0.81. This high annual morbidity rate probably represents an overestimate as it is based on the assumption that the 6-month observation period is representative of the year.

TABLE 5. MEAN DURATION OF MIDDLE EAR EFFUSION IN 404 CHILDREN COMPUTED WITH RISK FACTOR

Time Period (mo)	*New Cases (Risk = i)*	*Recovered Cases (Risk = r)*	*Mean Duration (1-r)/r*
0-1	29/326 = 0.089	28/78 = 0.359	1.79
1-3	31/325 = 0.095	39/79 = 0.494	1.02
3-6	44/333 = 0.132	32/71 = 0.451	1.25

Mode of Calculation, Ears/Children. The results could be based on calculation for each ear separately. Another possibility was calculation for each child with the poorer ear representing the child. This method would yield considerably higher morbidity rates because children with unilateral MEE would be weighted equally with children having MEE bilaterally (Table 3). In characterizing the course of the disease with repeated tests, it is simpler to evaluate each ear separately. But from an epidemiological point of view, and in the clinical situation too, the important consideration is whether something is the matter with the child. However, the question is still unsettled regarding whether the course of MEE in a child affected by continuous disease of the same ear is identical with that in a child affected with middle ear disease in changing ears. These problems were studied retrospectively starting with the data at the end of the observation period (February 1979) and comparing the results in each case at the three preceding tests (Table 6). The analysis, comprising multiconditioned paired variables, was carried out for 1) all right ears separately, 2) all left ears separately, and 3) for each child a) affected unilaterally and in the same ear each time, b) affected unilaterally but varying in side from test to test, c) varying between unilateral and bilateral disease, and d) affected bilaterally at all tests. After simplifying history into scores from 0 to 4 as shown in Table 6, the risk of having the disease at the end of the observation period was described graphically (Fig 4). Applying a maximum likelihood method, the formula $Fx = 0.1028\ (1.6524)^x$ described the observation (goodness of fit X^2 test, $p = 0.416$ with 22 df). The risk of MEE at the end of the observation period was heavily conditioned by the history, but evenly so in all three events (Fig 4). Thus, the frequency increased from about 10% in ears/children with no MEE at any of the previous tests to about 80% in those who had exhibited MEE at all previous tests.

TABLE 6. MIDDLE EAR EFFUSION IN 404 CHILDREN IN FEBRUARY 1979 AND MORBIDITY PROFILES AT PRECEDING TESTS

Month				*Frequency in February 1979*								
				Right Ears			*Left Ears*			*One or Both Ears*		
A	*S*	*N*	*Score*	+	*Total*	%	+	*Total*	%	+	*Total*	%
0	0	0	0	36	321	11.2	25	295	8.5	35	273	12.8
+	0	0	1	2	13	15.4	2	19	10.5	2	21	9.5
0	+	0	1	0	10	0	3	18	16.7	2	21	9.5
+	+	0	2	3	12	25.0	6	18	33.3	5	18	27.8
0	0	+	2	3	17	17.7	6	19	31.6	8	24	33.3
+	0	+	3	1	5	20.0	4	8	50.0	3	7	42.9
0	+	+	3	5	8	62.5	4	9	44.4	3	8	37.5
+	+	+	4	15	18	83.3	14	18	77.8	25	32	78.1
			Total		404			404			404	

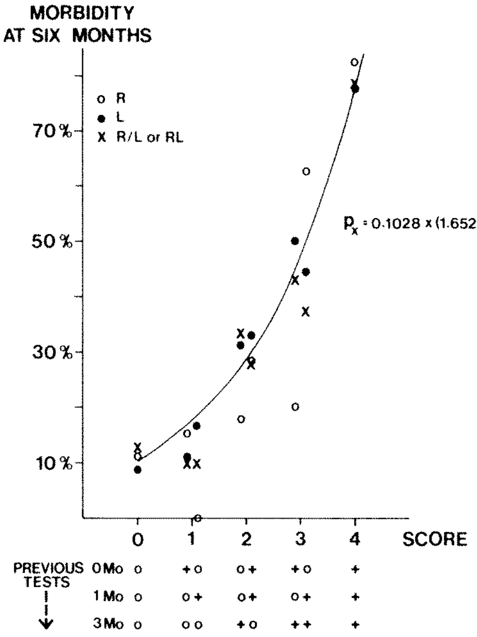

Fig 4. Conditioned probability of MEE at end of observation period as a function of scored morbidity on preceding three tests in 404 children. R - Right ears; L - Left ears; R/L - Either right or left ears; RL - Both right and left ears; o - Absence of middle ear effusion; + - Presence of middle ear effusion.

Figure 4 also shows that cases normal at the first three tests (000) had approximately a 10% risk of developing MEE at the 6-month test, which is essentially the same risk as those who exhibited isolated MEE at an earlier observation time (+ 00 and 0 + 0). In other words, a single, rapidly transient episode of MEE did not increase the risk of recurrence, whereas a pattern of recurrent MEE had a distinctly poorer prognosis.

IMPLICATIONS

To the clinician the high frequency and short average duration of MEE mean that an initial episode of secretory otitis media in young children, either as a chance finding or in a child with middle ear symptoms, should not immediately be treated surgically, if at all. On the other hand, such a finding always indicates follow-up which should be continued for at least 3 months before therapeutic efforts are undertaken (Figs 3 and 4). In a clinical situation, follow-up is proposed at similar intervals to those in this study. Classification of individual cases according to the paradigm in Figure 4 can then be used directly in weighing whether to intervene or to temporize, as this decision can be supported in each case by concrete probabilities of spontaneous resolution versus continued disease.

With a mean duration of approximately 3 months, the majority of MEEs were transient. This implies that any treatment has a marked placebo effect, which might be misleading in the absence of controls. Due to the highly fluctuating course of MEE, however, the criteria for a well-controlled study are extremely difficult to meet. Any assessment of a therapeutic effect in MEE requires critical attention to control measures in planning and performing the research projects as well as in evaluating results.

Identifying important middle ear disease as early in life as possible is desirable from several points of view,[12] and the possibilities of mass screening by impedance audiometry for this purpose have been ardently discussed with suggestions of prompt institution.[13] Lewis et al[14] were probably the first to show that an isolated tympanometric result was not a sufficient basis for classification. They proposed instead a retesting program which would enable a reasonable distinction between children with and without major middle ear problems. Today there is no disagreement concerning the necessity of repeated testing of the same child. Indeed, screening programs involving repeated testing have been instituted,[15] and recommendations have been made concerning criteria for impedance measurement in audiometric screening.[16]

According to the present study, however, the retesting principle does not solve the sorting problem, ie, identifying most middle ear disorders affecting young children and distinguishing transient from long-term problems. It expands the testing program beyond what may be practical and financially realistic. If we are content with pointing out the approximately 6% of the children in the present study who exhibited unchanged MEE from test to test, the strategic problems of the testing are, of course, not so enormous since this would involve the retesting only of successive failures. Retesting beyond the first 3 months does not appear useful (Figs 3 and 4) since the rate of spontaneous recovery declines at this point in time. Also, any retesting program at practical intervals will miss cases of new and recurring MEE which resolve between tests, ie, in which both onset and recovery occur during a period when no tests are done. Moreover, impedance testing cannot distinguish the severity of middle ear disorders. For these reasons it would probably not be a practical or productive test for mass screening of preschool children.

CONCLUSIONS

Repeated tympanometric screening of a geographically defined population of 3-year-old children revealed the following:

1. MEE is demonstrable by the impedance test with an accuracy of 97%.
2. Of all 3-year-olds in the series, 20% had MEE at any given time of testing, regardless of the season, but the children affected varied widely from test to test.
3. Forty-one percent of the children had at least one episode of secretory otitis media during the 6-month period, while only 6% had MEE

at all tests.

4. The morbidity data were not significantly different when calculated "per ear" versus "per child."
5. The chances of spontaneous recovery after a follow-up period exceeding 3 months were slight; thus, active intervention can be considered after a follow-up period of this length.

REFERENCES

1. Fiellau-Nikolajsen M. Tympanometry and middle ear effusions. A cohort-study of 3-year-olds. Int J Ped Otorhinolaryngol 1980; 2:39-49.

2. Holm VA, Kunze LH. Effect of chronic otitis media on language and speech development. Pediatrics 1969; 43:833-9.

3. Jaffe B. Hearing loss in children. Baltimore: University Park Press, 1977:378-80.

4. Fiellau-Nikolajsen M, Lous J, Pedersen SV, et al. Tympanometry in 3-year-old children: I. Scand Audiol 1977; 6: 199-204.

5. Fiellau-Nikolajsen M. Tympanometry in 3-year-old children: II. Scand Audiol 1979; 8: 181-5.

6. Tos M, Poulsen G. Tympanometry in 2-year-old children. ORL 1979; 41:1-10.

7. Tos M, Poulsen G, Hancke AB. Screening tympanometry during first year of life. Acta Otolaryngol (Stockh) 1979; 88: 388-94.

8. Fiellau-Nikolajsen M, Falbe-Hansen J, Knudstrup P. Tympanometry in 3-year-old children: III. Scand Audiol 1980; 9:49-54.

9. Haughton PM. Validity of tympanometry for middle ear effusions. Arch Otolaryngol 1977; 103:505-13.

10. Brooks DN. The use of the electro-acoustic impedance bridge in the assessment of middle ear function. Int Audiol 1969; 8:563-9.

11. Orchik DJ, Morff R, Dunn JW. Impedance audiometry in serous otitis media. Arch Otolaryngol 1978; 104:409-12.

12. Paradise JL, Smith CG. Impedance screening for preschool children. Ann Otol Rhinol Laryngol 1979; 88:56-65.

13. Feldman AS, Northern JL, Rosenberg J, et al. Communication. Ann Otol Rhinol Laryngol 1979; 88:738.

14. Lewis N, Dugdale A, Canty A, et al. Open-ended tympanometric screening: a new concept. Arch Otolaryngol 1975; 101:722-5.

15. Harford ER, Bess FH, Bluestone CD, et al, eds. Impedance screening for middle ear disease in children. New York: Grune & Stratton Inc, 1978.

16. Harford ER, Bess FH, Harrington DA, et al. Use of acoustic impedance measurement in screening for middle ear disease in children. Ann Otol Rhinol Laryngol 1978; 87:288-92.

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SECOND INTERNATIONAL TINNITUS SEMINAR

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ALTERATION OF AMINOGLYCOSIDE ANTIBIOTIC OTOTOXICITY: EFFECT OF SEMISTARVATION

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The effect of semistarvation on the toxicity and ototoxicity of tobramycin sulfate (TO) and gentamicin sulfate (GE) was investigated in guinea pigs by electrophysiological and histopathological methods. The presented data has shown that the toxicity and ototoxicity of aminoglycoside antibiotics is substantially increased when guinea pigs were semistarved. Our results should also warn researchers using semistarvation in their conditioning experiments which investigate the toxicity of different chemicals. Toxicity was greater in GE- than TO-treated animals, which caused the GE-treated animals to die during treatment or shortly after treatment. Thus, TO should be preferentially used because it has been shown to be less toxic and ototoxic in normal and altered nutritional conditions.

The toxicity of animoglycoside antibiotics is widely known, particularly in their effect on the kidney and the inner ear. Some of the factors which predispose to toxicity have been recognized, such as prolonged treatment or altered kidney function, but in many cases these factors cannot fully explain the development of toxic reactions. Because infections which require treatment by aminoglycoside antibiotics (Am An) occur in all age groups and in patients suffering from additional diseases, the nephrotoxicity and ototoxicity resulting from such therapy may be the result of several interacting factors. In our society the elderly are the principal drug uses, because aging is often associated with chronic disease (congestive heart failure, diabetes mellitus and cancer) which can reduce or alter appetite and thus cause malnutrition or possible decrease of nutrient utilization. Often patients with chronic renal failure have a decreased concentration of plasma proteins, which may result in more free nonprotein bound drugs. Nutritional requirements are further altered in women using contraceptives. Malnutrition is very common among alcoholics, narcotics users and other drug addicts, food faddists and depressed patients. Clinical malnutrition may be precipitated by an infection or complicated by anemia. Protein-calorie malnutrition has been found to be quite frequent among hospitalized patients.[1-4] In a recent study Willard et al[5] reported that 31.5% of 200 hospital-admitted patients were malnourished.

In the past the influence of nutritional deficiency upon drug metabolism and toxicity has not been investigated systematically. There are no data concerning nutritional effects on aminoglycoside toxicity and ototoxicity.

METHODS

Twenty-four healthy guinea pigs, predominantly males weighing between 250 and 350 g, were divided into five groups. All animals were given water ad libitum. The amount of available food was restricted to one third of normal consumption for groups 1, 4 and 5, while groups 2 and 3 were given food ad libitum. Prior to our experiments, food consumption was recorded daily for a large group of guinea pigs for 14 days. The measured amount was related to the body weight of each guinea pig and then averaged for all guinea pigs and all days. A value of 0.025 g food/g body weight was determined to be the normal daily consumption. This value was then used to calculate one third of the daily requirements for each guinea pig using the weight of the animals at the beginning of the experiment. All animals were fed with "lab chow" (Purina Co). Group 1 was not treated with antibiotics. Groups 2 and 4 were treated with tobramycin sulfate (TO) 200 mg/kg/day for seven days. Groups 3 and 5 were treated with gentamicin sulfate (GE) 200 mg/kg/day for seven days. Both drugs were administered intramuscularly. Their dosage of salt form was calculated and adjusted daily during the treatment period according to their body weight. In all animals ototoxicity was evaluated histologically. Only the animals with TO had a round window electrode implanted and a reference electrode placed subcutaneously in the dorsal portion of the neck. Both electrodes were connected to a socket fastened to the skull with four screws and dental acrylic cement. The cochlear microphonics (CM) and action potentials (AP) were recorded before, during and after the treatment. Both cochlear potentials were elicited by 1 and 8 kHz 15 ms tone pulses. The intensity of stimuli was calibrated by B & K sound level meter and is related to the reference pressure of 0.0002 dynes/cm^2 at 1000 Hz. The rise time of the stimuli was adjusted by electronic filter to eliminate acoustical click from receiver. Both AP and CM were amplified, averaged and the resulting potentials displayed on an oscilloscope. The cochlear potentials were tested in animals placed on a very small elevated platform. The construction and use of this device was described earlier.[6] Because of the animal's natural fear of falling they sat in one spot relatively motionless during the testing, thus alteration of potentials by movement was minimized. Also because the testing was in a free field, the requirement that the animals were tested each time by the same sound intensity was fulfilled by the elimination of animal movement. Three weeks after the end of the treatment all animals were sacrificed and the inner ears were fixed with Millon-

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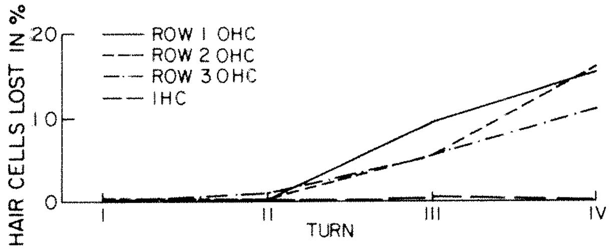

Fig. 1. (Group 1) Loss of OHC and IHC in turns and rows. All animals had free access to water, but amount of food was reduced to one third of average consumption; they were not treated.

ing buffered osmium tetroxide for two hours in the refrigerator. Before dehydration and dissection, the cochlea was decalcified in about 25 ml of 5% ethylenediamine tetraacetic acid (EDTA) phosphate-buffered solution in room temperature for 48 hours. Dissected tissue was mounted in glycerin and the degree of histopathological changes (missing hair cells) calculated in each turn (300 outer hair cells [OHC] and 100 inner hair cells [IHC]). All electrophysiological and histopathological data were statistically evaluated and graphs were constructed according to the mean and standard error of mean.

RESULTS

Group 1. The guinea pigs in this group were not treated with Am An, they had free access to water, but their food was reduced to one third of average consumption which corresponded to 0.025 g/g of body weight. In this group only histological changes were evaluated. None of the four animals died during the experiment. Histopathological evaluation showed a small increase of OHC loss in the apical turns (III and IV) of all three rows (Fig. 1), when compared with the nontreated controls fed ad libitum.

Group 2. The animals in this group were treated with TO 200 mg/kg/day (once a day) for seven days, but had free access to food and fluid and thus were considered as treated controls. None of the seven guinea pigs died during the treatment, but two died one week after the end of treatment. The CM did not show significant changes in amplitude (Fig. 2). The changes in AP, because of large differences between animals, were not significant (Fig. 3). Histopathological changes (missing OHC) were most pronounced in all three rows of the first turn where they reach 38.9% ± 12.2 to 42.1% ± 13.3 and in the first row of the second turn 33.8% ± 10.5. Also the IHC were damaged, particularly in the third and fourth turns 15.7% ± 10.5 and 18.4% ± 12.2 respectively (Fig. 4).

Group 3. The guinea pigs were treated with GE in the same dosage as TO in the previous groups (200 mg/kg/day) for seven days. They also had free access to food and water and were thus considered as treated controls for GE. In this group only 1 of 4 animals lived to the end of the experiment, 1 died on the 12th and 2 died on the 18th day of the experiment. For histopathological evaluation, only the animals living to the 18th day and 28th day of the experiment were used. Histopathological damage was largest in the first and second turns, 60-63% and 50.75-68.6% respectively (Fig. 5). The largest number of IHC missing was in turn II 22.7% ± 22.7. However, total damage would probably have been larger had all the animals lived at least three weeks after the treatment.

Group 4. This group received a single 200 mg/kg dose of TO daily for seven days. They had free access to water but received only one third of the food they normally consumed. In this group only 1 of 7 guinea pigs died one week after the end of treatment. Small increases of CM and AP were observed during the first several days of treatment, but after seven days all potentials rapidly declined, and this decline continued to the end of the experiment (Figs. 2 and 3). Histopathologic changes observed in surface preparations were very extensive. Pronounced OHC loss was observed in the first row of turns I, II, III and IV. Damage was 91.64% ± 5.5, 96.54% ± 25, 100% ± 0 and 90.6% ± 6.3 respectively. In the second row damage of turns I, II and III was also very extensive, OHC were missing in 89.2% ± 7.1, 86.1% ± 9.6 and 68.3% ± 10.1 respectively. Damage of IHC was highest in turn IV 98.7% ± 0.57. The number of missing IHC declined toward the turn I where it was smallest 7.4% ± 4.2 (Fig. 6).

Group 5. This group was treated with GE 200 mg/kg/day for seven days. These animals had free access to water but were limited in food intake to one third of their expected consumption. All ani-

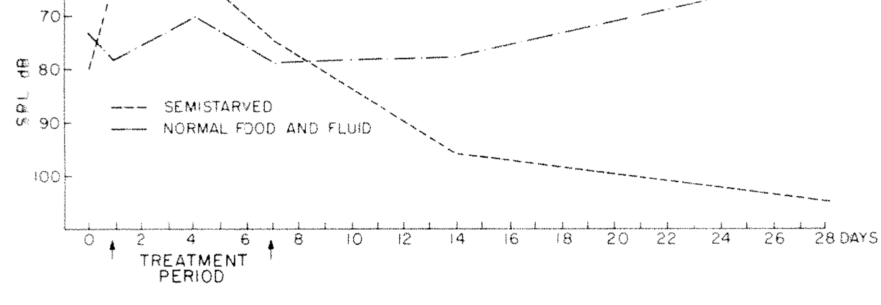

Fig. 2. Composite diagram of CM threshold changes elicited by 1-kHz tone in guinea pigs treated with TO 200 mg/kg/day for 7 days (1 time a day).

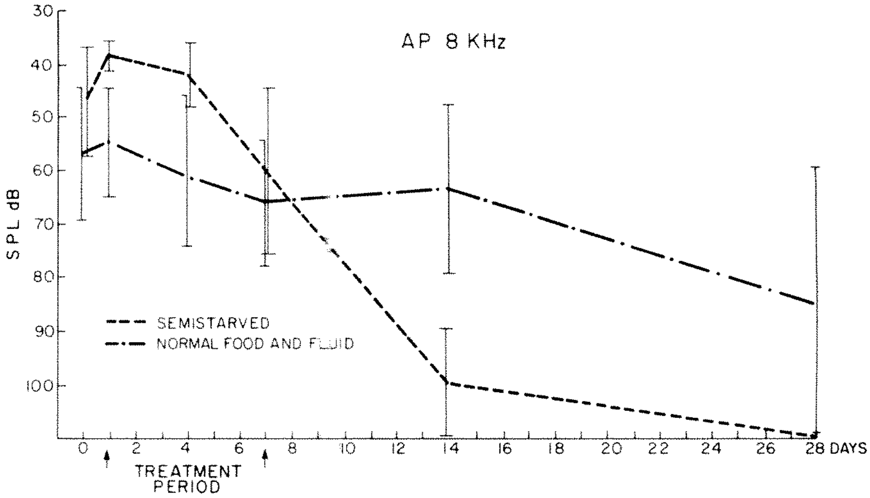

Fig. 3. Composite diagram of threshold changes of action potentials elicited by 8-kHz tone during and after treatment with TO 200 mg/kg/day for 7 days (1 time a day). Vertical bars represent standard error of mean.

mals (4) in this group died during or shortly after the treatment. Histopathological data which are available from the animals which died between the 6-10 days of the experiment showed greater damage (Fig. 7) than group 3 three weeks after treatment. However if these animals had lived for the whole experiment, damage in the inner ear would have been probably close to 100%.

In all animals, the body weight, hematocrit, blood urea nitrogen, and serum level of antibiotics were also noted. These results will be published elsewhere at a later date.

Data presented in this study showed the semistarvation substantially increased the toxicity of both TO and GE. This toxicity was more apparent in GE-treated guinea pigs, which died during the treatment or shortly after the treatment, than in TO-treated guinea pigs.

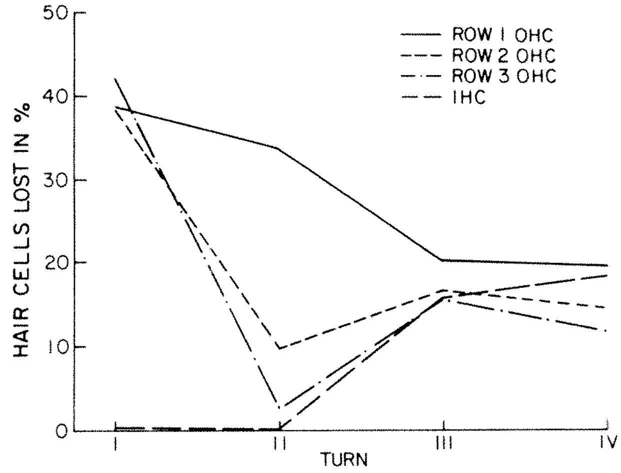

Fig. 4. Loss of OHC and IHC in rows and turns after treatment with TO 200 mg/kg/day for 7 days (1 time a day). All animals had free access to food and water. (From Prazma J, Ferguson SD, Kidwell SA, Harrison HG, Drake A, Fischer J. Alteration of aminoglycoside antibiotic ototoxicity by hyper and hypohydration. Am J Otolaryngol 1981; 2:299-306. Reprinted with permission.)

DISCUSSION

The process of eliminating drugs from the body is dependent on factors such as biotransformation of the drugs, binding to plasma and tissue proteins, and renal clearance. The activities of enzymes involved in metabolizing drugs have been shown to be dependent on nutritional status. Protein deficiency has a substantial effect on this capacity, particularly with drugs metabolized in the liver. Protein deficiency can also influence mitochondrial and microsomal phospholipids, leading to an increase of phosphatidylethanolamine and a decrease of phosphatidylcholine which is essential for electron transfer and oxidation of different drugs.[7,8] Aminoglycoside antibiotics are not metabolized but are excreted by glomerular filtration of the kidney unchanged.

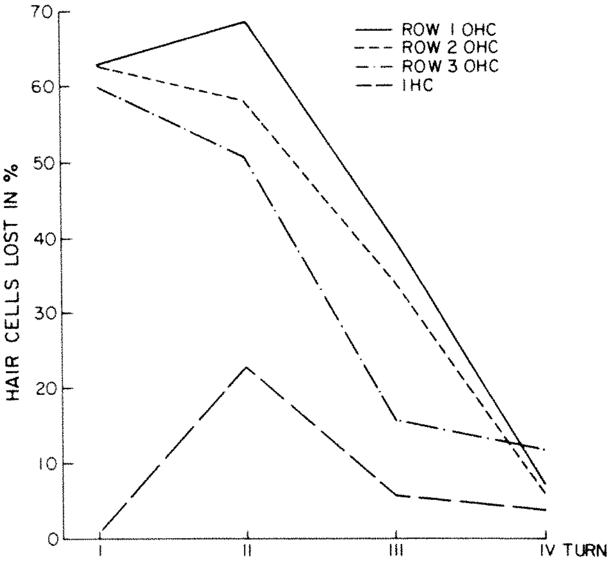

Fig. 5. (Group 3) Loss of OHC and IHC in rows and turns after treatment with GE 200 mg/kg/day for 7 days (1 time a day). All animals had free access to food and water. (From Prazma J, Ferguson SD, Kidwell SA, Harrison HG, Drake A, Fischer J. Alteration of aminoglycoside antibiotic ototoxicity by hyper and hypohydration. Am J Otolaryngol 1981; 2:299-306. Reprinted with permission.)

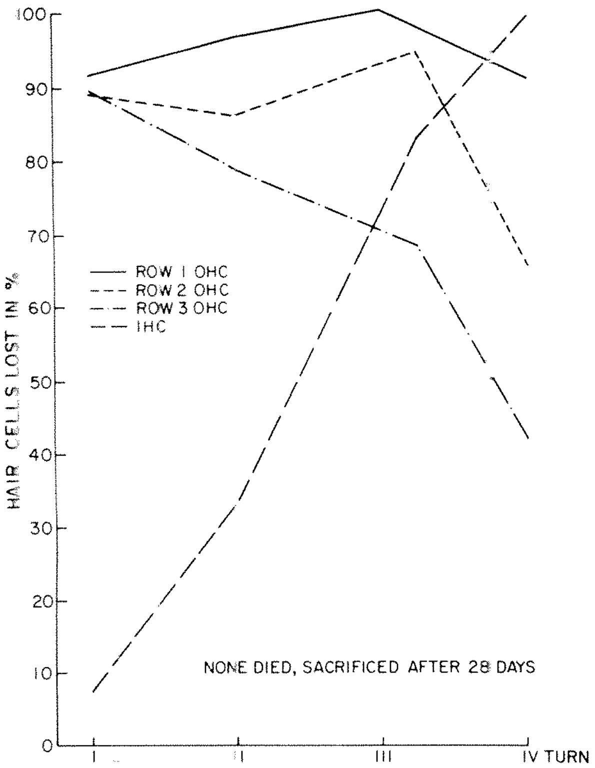

Fig. 6. (Group 4) Loss of OHC and IHC in rows and turns after treatment with TO 200 mg/kg/day for 7 days (1 time a day). All animals had free access to water but amount of food was reduced to one third of average consumption.

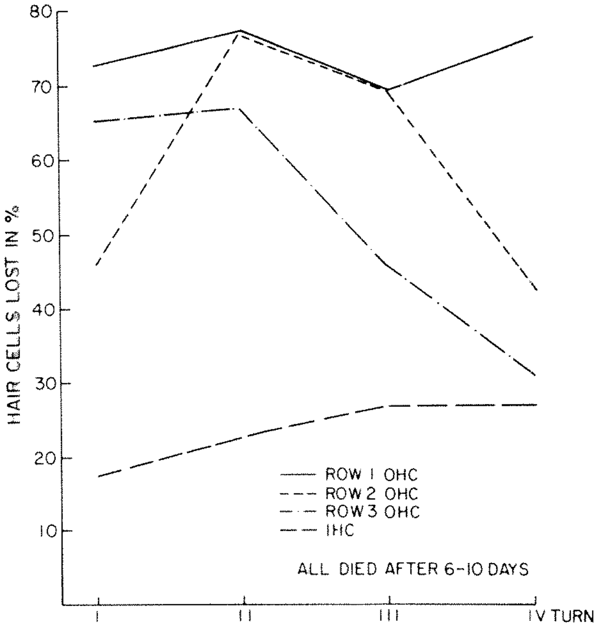

Fig. 7. (Group 5) Loss of OHC and IHC in rows and turns after treatment with GE 200 mg/kg/day for 7 days (1 time a day). All animals had free access to water but amount of food was reduced to one third of average consumption. This data represents histopathological changes not after 28 days as they are in all other groups, but after 6-10 days when all animals died.

No difference in streptomycin pharmacokinetics (plasma concentration, plasma half-life, binding to plasma protein, or urinary excretion) was found when malnourished and well-nourished individuals were compared.[9] However, Mehta et al[10] in a study on children suffering from protein-calorie malnutrition has reported higher peak plasma levels and delayed absorption and excretion of chloramphenicol. Protein-calorie-malnourished children also showed significant changes in half-life, protein binding and distribution of tetracycline when compared with well-nourished individuals.[11]

Semistarvation has been found to reduce glomerular filtration and renal plasma flow rate.[12,13] This observation may explain the increased toxicity of Am An in our experiments. Decreased glomerular filtration during semistarvation will increase the plasma level of Am An and thus increase their level in cochlear fluids and augment their toxic effect on hair cells.

Our presented data has shown that toxicity and ototoxicity of aminoglycoside antibiotics is significantly increased when guinea pigs were semistarved. Thus, proper nutrition should always be maintained during treatment with Am An. This observation should also be brought to the attention of toxicologists who use food deprivation in classical conditioning. Food deprivation in their experiments may enhance investigated toxicity and thus distort the experiment and lead to misleading results. In our experiments tobramycin sulfate is shown to be significantly less toxic and ototoxic than gentamicin.

ACKNOWLEDGMENT — The secretarial assistance of Lynette Imrick is acknowledged.

REFERENCES

1. Bistrian BR, Blackburn GL, Hallowel E, et al. Protein status of surgical patients. JAMA 1974; 230:858-60.

2. Butterworth CE. Skeleton in the hospital close . Nutr Today 1974; 9:4-8.

3. Bistrian BR, Blackburn GL, Vitale J, et al. Prevalence malnutrition in general medical patients. JAMA 1976; 235: 1567-70.

4. Weinsier RL, Hunker EM, Krumdieck CL, et al. A prospective evaluation of general medical patients during the course of hospitalization. Am J Clin Nutr 1979; 32:418-26.

5. Willard MD, Gilsdorf RB, Price RA. Protein-calorie malnutrition in a community hospital. JAMA 1980; 243:1720-2.

6. Prazma J, Orr JL, Kidwell SA. Device for nonstressful restraining of rats and guinea pigs. Physiol Behav 1980; 24:155-6.

7. Rogers CG. Lipid composition and metabolism in liver mitochondria and microsomes of rats fed a low protein diet. J Nutr 1971; 101:1547.

8. Parke DV. The interaction of food and "foreign" substances: the effects of diet and nutrition on the metabolism of drugs. R Soc Health J 1978; 98:256-61.

9. Prasad JS, Krishnaswamy K. Streptomycin pharmacokinetics in malnutrition. Chemotherapy 1978; 24:333-7.

10. Mehta S, Kalsi HK, Jaya Raman S, Mathur VS. Chloramphenicol metabolism in children with PCM. Am J Clin Nutr 1975; 29:977-81.

11. Shastri RA, Krishnaswamy K. Undernutrition and tetracycline half-life. Clinica Chim Acta 1976; 66:157-64.

12. Alleyne GA. The effects of severe protein calorie malnutrition on the renal function of Jamaica children. Pediatrics 1967; 39:400-11.

13. Ichikawa I, Purkerson ML, Klahr S, et al. Mechanism of reduced glomerular filtration rate in chronic malnutrition. J Clin Invest 1980; 65:982-8.

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INTERNATIONAL CONFERENCE ON HEAD AND NECK CANCER

The Society of Head and Neck Surgeons and the American Society for Head and Neck Surgery are sponsoring an International Conference on Head and Neck Cancer to be held July 22-27, 1984, in Baltimore, Maryland. The program will provide a comprehensive presentation of the present status and recent results of basic research and treatment in head and neck cancer. Abstracts are invited for oral presentations and scientific exhibits. For further information contact the Program of Continuing Education, University of Maryland School of Medicine, 10 South Pine Street, Baltimore, Maryland 21201.

Ann Otol Rhinol Laryngol 92:1983

BRAINSTEM EVOKED RESPONSE AUDIOMETRY

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Brainstem evoked response audiometry is useful in the identification of threshold levels as well as in the diagnosis of eighth nerve tumors. The instrumentation is a modification of the electroencephalograph and an averaging computer: 3,000 clicks, 16/s, are presented and averaged for each printed response. Evoked responses can be obtained from a patient who is unable or unwilling to respond to conventional behavioral testing; best results are obtained from quiet or asleep patients.

INTRODUCTION

Evoked response audiometry has been an important clinical tool in the diagnosis of particular types of hearing loss over the past few years; it is especially useful for the patient who is difficult to evaluate with behavioral audiometry.[1] Acoustic stimulation of the cochlea produces an evoked electrical response in the central nervous system which can be recorded by the use of scalp electrodes yielding information equally as reliable as that obtained from electrodes placed in the middle ear.[2] It has been evident during lectures that a simple presentation of the basics of this subject will assist in the appreciation of this procedure.

The anatomical structures of the brainstem generating these responses are the auditory nerve which generates waves I and II, the superior olivary complex which generates wave III, the nucleus of the lateral lemniscus which generates wave IV, the inferior colliculus which generates wave V, the medial geniculate body which generates wave VI, and the auditory radiations to the cerebral cortex which generate wave VII.[3,4] The passage of electrical stimuli through these tracts produces responses with an unvarying time delay which may be correlated with the curves produced. The integrity of the anatomical structures can be identified by the time interval of generated electrical response. The time required for passage of the electrical impulse from one anatomical structure to the next is exact and the responses obtained are described as "time-locked." These and their relation to the time of passage are seen in Figure 1.

METHODS

Equipment. The equipment used in the collection of these data is a modification of the electroencephalograph; in addition an averaging computer to analyze the responses of multiple stimulations of the auditory system is employed (Fig. 2).

Stimulus. The acoustic stimulus is a click applied 16 times per second for three minutes allowing 3,000 clicks to stimulate the ear. Maximum click level in this testing unit is 81 dB hearing level.

Averaging Computer. In a single evoked response trace, the appearance is that of a random wave often described as a background noise. When the computer is used to average many tracings, those responses which are time-locked to the acoustic stimulus will be summed by the computer in linear fashion and by the square root of the number of sweeps of any response not time-locked. The resultant plot of this information produces a series of curves which demonstrate the time-locked responses as visible peaks above the baseline. Increased amplitude of the response curve is seen with increasing numbers of stimuli or increasing intensity levels (Figs. 3 and 4).

Classification of Auditory Evoked Potentials. Auditory evoked potentials are classified by the time, in milliseconds, in which the response occurs. These represent the anatomical structures which generate the neural responses. The components of the evoked responses in relation to their occurrence as time-locked events[5] are 1) early (0-10 ms: auditory nerve and brainstem), 2) middle (10-50 ms), and 3) late (50-150 ms).

Technique. It is most practical to sedate children between 4 months and 7 years of age for this examination in order to eliminate muscle artifact from the resultant trace. The sedation should be, above all, safe, and should, in addition, be short-acting and effective. It should neither alter the evoked response nor the background activity so that the residual unaveraged electroencephalogram does not obscure the underlying averaged evoked potential. Chloral hydrate is given orally and is usually satisfactory. If for some reason it cannot be utilized, intravenous barbiturates, rectal pentothal and/or halothane and nitrous oxide given by an anesthesiologist may be the method of choice. The early components give the most useful information because they are altered little by the medication. The later responses may be useful since they can be recorded in sedated children and do identify cortical function.

Three gold-plated cup electrodes are attached to the head, forehead, vertex and ipsilateral mastoid. Stimulation of the ears can be accomplished under earphones monaurally or binaurally, or by a speaker in a free field.

The stimulus (3,000 clicks) is presented and responses are averaged for one to five different intensity levels. SYNAP I produces a printed record for averaged responses to 3,000 clicks.

DISCUSSION

Only the early components measure brainstem responses. Latency of response is measured in milliseconds between onset of stimulus and the seven positive peaks of response. If the electrodes are reversed, negative peaks (valleys) become the significant parts of the curve. All seven brainstem responses occur within 10 ms after stimulation. These

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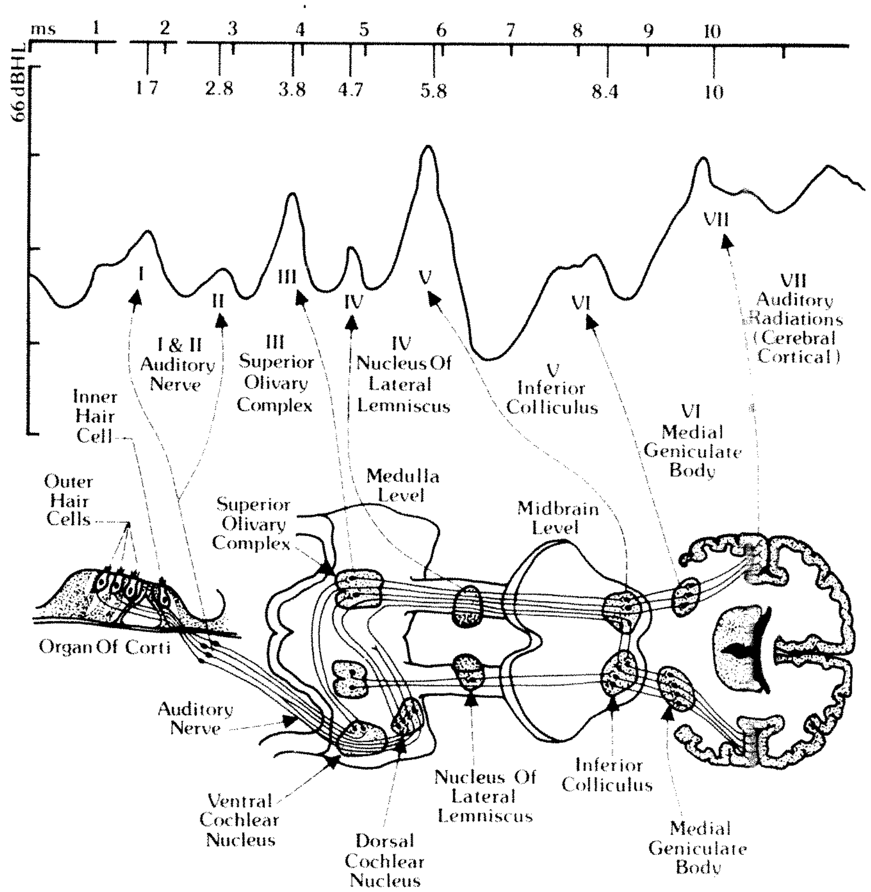

Fig. 1. Anatomical structures between organ of Corti and cerebral cortex and their relationship to responses obtained by measurement of evoked potentials. (Modified with permission[4])

responses are known as the early components of auditory evoked potentials.

There is a distinct effect seen when the intensity of the stimulus is varied. The greater the intensity, the shorter the latency of all peaks (Fig. 5). The intervals between peaks, however, remain unchanged at different intensity levels suggesting that these depend on normal propagation of the neural impulse and are called interpeak latencies. The prolonged latencies of all peaks resulting from lower intensity stimulation suggest that intensity-related latency changes occur in the cochlea. This phenomenon is also seen with conductive hearing losses which reduce the intensity of the signal to the cochlea.[6-8] This measurement of interpeak latency should be made from peak I to peak V.

Eighth nerve tumors may cause an intrapeak latency increase after peak I. This intrapeak latency difference demonstrates delay in the occurrence of response curves and is evaluated by measurement of delay seen at peak V. The response delay is seen by comparing the difference of latency between the two ears (Fig. 6). Cochlear delay is unimportant in evaluating an eighth nerve tumor. However, when the stimulus is maintained at a constant sensation level and the responses of one ear are compared to the responses of the other, a difference in interpeak latency indicates impairment of nerve conduction and is suggestive of a tumor impinging on the eighth nerve. The interval latency difference between ears is normally less than 0.2 ms but was 0.4 ms or greater for 35 acoustic tumor cases and for 7 of 10 other temporal bone tumors.[7]

Acoustic tumor size can be estimated by measuring interpeak latency delay. A large tumor with greater compression of the nerve produces more in-

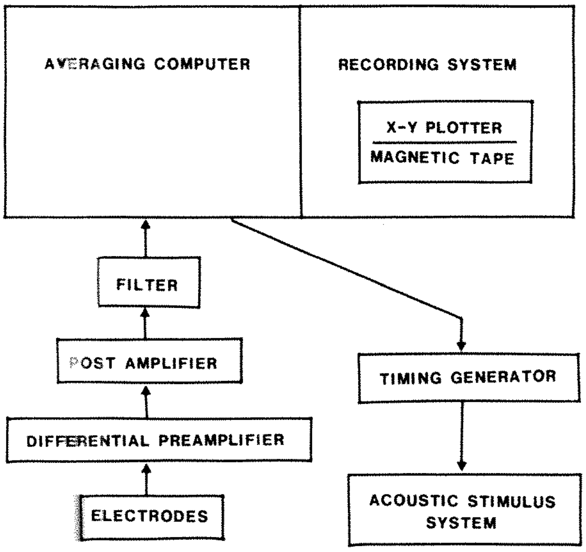

Fig. 2. Arrangement of components of SYNAP I signal-averaging evoked response system (Infant Hearing Assessment Foundation).

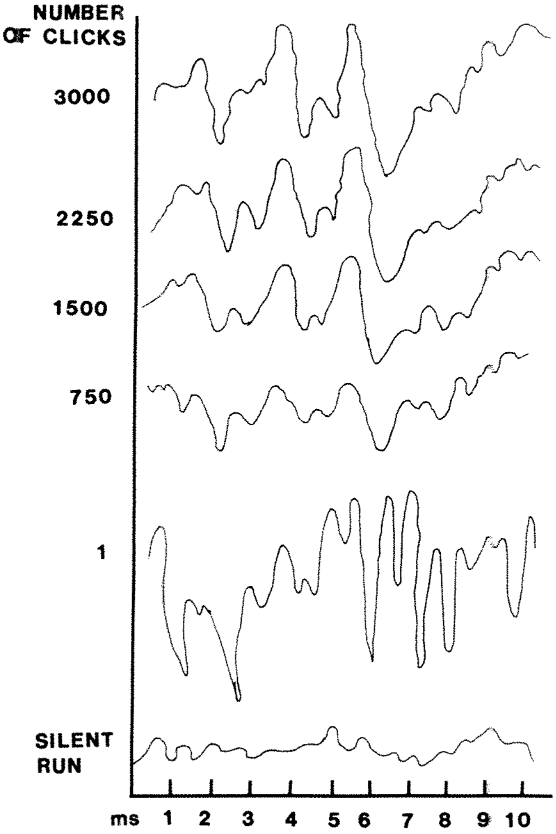

Fig. 3. Tracings of evoked responses showing increasing amplitude of response curves with increasing number of stimuli.

terference with nerve conduction; therefore, the nerve conduction time is increased. It has been found that variation of latency between ears in any individual is within 0 to 0.4 ms and that an interpeak latency variation of more than 0.2 ms suggests the presence of a tumor. It has been determined that peak V is best used for measuring this variation in interaural testing as it is the strongest and most reliably recorded.[5]

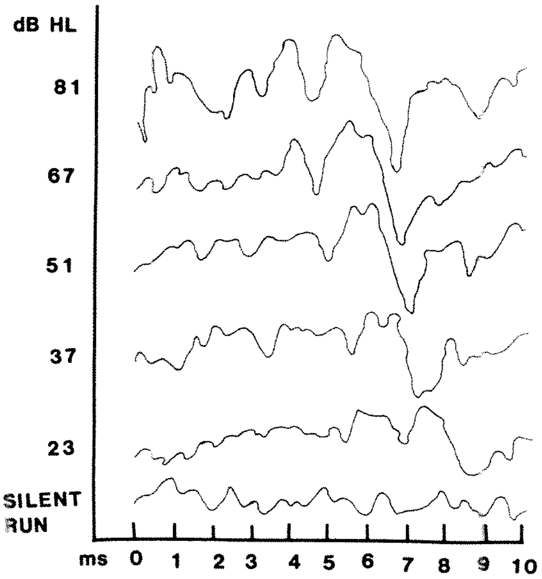

Fig. 4. Tracings of evoked responses showing increasing amplitude of response curves with increasing intensity levels.

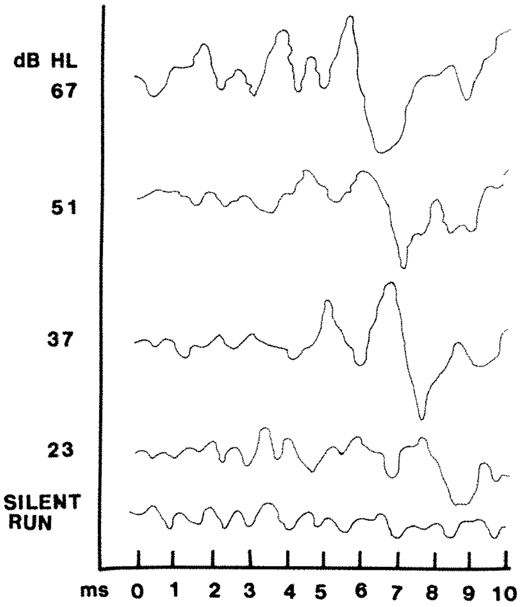

Fig. 5. Tracings of evoked responses showing decreasing latency of peaks with increasing intensity of stimulus.

Multiple sclerosis affects neural transmission of electrical impulses. The tracing of averaged responses in these patients is characterized by erratic waveform and lack of reproducibility of consecutive brainstem evoked waveforms (Fig. 7).[9]

Hearing aid evaluation is another important use of brainstem evoked response audiometry. The choice of an appropriate amplification system is extremely difficult in infants and small children. Brainstem evoked response audiometry can provide tracings of the delayed peak V without amplification. When an aid is coupled to the ear and stimulated in the sound field, the resultant tracing shows peak V closer to normal latency. The threshold of peak V with aid is an important measurement assisting in selection of an appropriate hearing aid.

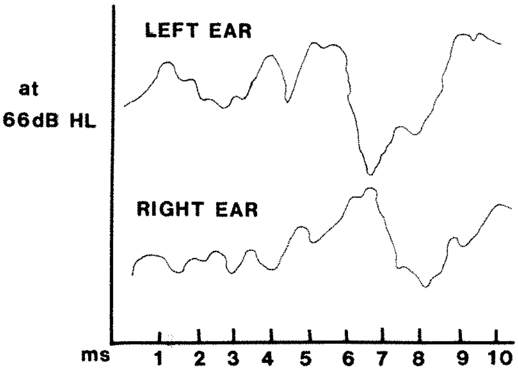

Fig. 6. Tracings of evoked responses showing latency difference of peak V between ears in patient with acoustic neuroma.

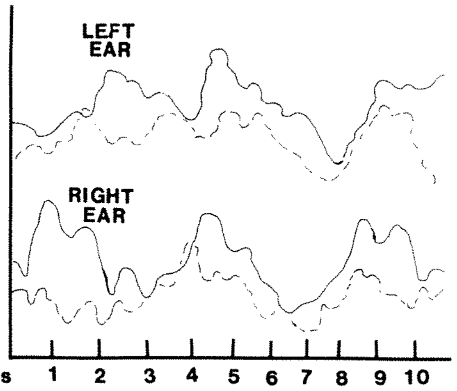

Fig. 7. Tracings of evoked responses showing characteristic erratic waveform and lack of reproducibility of consecutive waveforms in patient with longstanding multiple sclerosis. Solid line - First test; Dashed line - Repeat test.

Evoked Response Threshold. Determination of auditory threshold by means of the evoked response technique is simple and straightforward. These determinations may be made during sleep, but must be made with a quiet subject to eliminate excessive random "noise" of the electroencephalographic tracing and of muscle artifact, which complicate interpretation of the resultant traces.

In adults these evoked potentials can be identified at 10-20 dB above behavioral threshold. Although the threshold is elevated when compared to behavioral audiometry, excellent objective responses may be obtained either during natural sleep or under sedation. It is a great advantage to be able to test children and infants during sleep since elimination of muscle artifact greatly enhances the reliability of the final trace. There is essentially no difference between the evoked responses of the sleeping and awake subject. In infants the difference between brainstem evoked response threshold and behavioral threshold is even greater than in adults. The latency of response decreases from prematurity to infancy and continues to decrease during childhood (Fig. 8).[10]

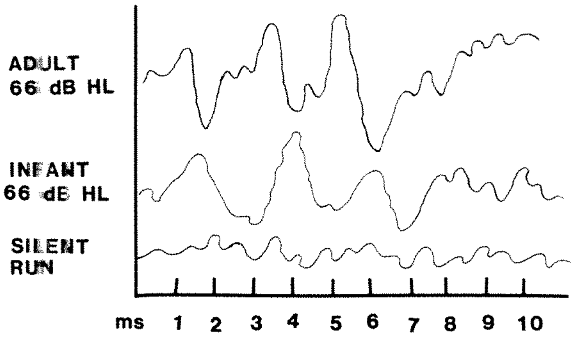

Fig. 8. Tracings of evoked responses showing decreasing latency of peaks with increasing age.

CONCLUSION

Brainstem evoked response audiometry is of particular use in subjects who are unable to make appropriate behavioral responses; evoked responses are recorded as objective written tracings. It is applicable to the newborn infant, small children, mentally retarded, the uncooperative, those suspect for cerebellopontine angle tumors, especially eighth nerve tumors, and multiple sclerosis. From this group come the patients most difficult to accurately assess audiometrically, so information obtained from these studies is of inestimable value in the management of their problems.

In most instances, except in the case of eighth nerve tumors and multiple sclerosis, the threshold determined by this method is the crucial item. In the evaluation of eighth nerve tumors, increased latency of response for peak III to peak V, when comparison is made between the two ears of the same individual, is the criterion by which the test result is evaluated. If the latency in one ear is significantly increased when compared to the contralateral ear, it has an extremely high correlation with the presence of an eighth nerve tumor. Multiple sclerosis and other demyelinating processes affect the neural transmission. The responses obtained in these patients are not reproducible and are therefore unstable.

REFERENCES

1. Lyons GD, Berlin CI, Lousteau RJ, et al. Electrocochleography with retardates. Laryngoscope 1974; 84:990-7.

2. Jewett DL, Williston JS. Auditory evoked far fields averaged from the scalp of humans. Brain 1971; 94:681-96.

3. Møller A, Peter J, Bennett M, Møller M. Intracranially recorded responses from the human auditory nerve: new insights into the origin of brainstem evoked potentials (BSEPs). Electroencephalogr Clin Neurophysiol 1981; 52:18-27.

4. Stockard JJ, Stockard JE, Sharbrough FW. Detection and localization of occult lesions with brainstem auditory responses. Mayo Clin Proc 1977; 53:761-9.

5. Davis H. Principles of electric response audiometry. Ann Otol Rhinol Laryngol 1976; 85 Suppl 28.

6. Glasscock ME III, Jackson CG, Josey AF, et al. Brainstem evoked response audiometry in a clinical practice. Laryngoscope 1979; 89 1021-35.

7. Selters WA, Brackmann DE. Acoustic tumor detection with brainstem electric response audiometry. Arch Otolaryngol 1977; 103:181-7.

8. Stockard J, Stockard JJ, Westmoreland BF, Corfits J. Brainstem auditory evoked responses. Arch Neurol 1979; 36: 823-31.

9. Martin ME, Moore EJ. Scalp distribution of early (0 to 10 msec) auditory evoked responses. Arch Otolaryngol 1977; 103: 326-8.

10. Mokotoff B, Schulman-Galambos C, Galambos R. Brainstem auditory evoked responses in children. Arch Otolaryngol 1977; 103:38-43.

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PERIPHERAL BLOOD T AND B LYMPHOCYTE SUBPOPULATIONS IN BELL'S PALSY

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A prospective clinical, virological and immunological study was performed on 25 consecutive Bell's palsy (BP) patients. Multiple cranial nerve involvement was found in 15 patients. A significant decrease in the peripheral blood T lymphocyte percentage as well as an increase in B lymphocyte percentage ($p < 0.001$) were found in 13 of the BP patients during the first 24 days from the clinical onset of the paralysis. No correlation was found between the peripheral blood lymphocyte subpopulations and the patient's age, sex, degree of paralysis or recovery rate. No changes were detected in the levels of immunoglobulins (IgG, IgM), complement (C_3, C_4) and antiviral antibodies to herpes simplex and zoster, EBV, cytomegalic virus, adenovirus, influenza and mumps. The clinical and immunological data of BP show a similar pattern to those of Guillain-Barre syndrome suggesting that BP may be an antoimmune demyelinating cranial polyneuritis which may be caused by a preceding viral infection.

INTRODUCTION

Bell's palsy (BP) is considered an acute idiopathic demyelinating peripheral neuropathy of the facial nerve. Histopathological and experimental studies lend support to this concept.[1-3] Clinical data accumulated in recent years indicate that BP is in fact a polyneuropathy since the facial paralysis is frequently associated with ipsilateral involvement of other cranial nerves.[4-6]

The last decade was enriched with studies concerning the role of viruses and immune responses in the etiopathogenesis of demyelinating diseases of both the central and peripheral nervous systems.[7-10] Involvement of viruses and immune mechanisms were also proposed in BP suggesting that it may be an autoimmmune postviral disease or due to reactivation of a latent herpes simplex virus.[6,11,12] However, the etiology and pathogenesis of BP are still an enigma.

In this prospective clinical, virological and immunological study of BP an immune response was found to participate, suggesting that both a viral infection and an autoimmune response may be involved in the etiology and pathogenesis of Bell's palsy.

MATERIAL AND METHODS

Thirty consecutive patients with peripheral facial nerve paralysis were studied prospectively. The evaluation according to a protocol included:

1. Clinical history and specific anamnestic details regarding the paralysis, and a complete physical, ENT and neurological examination.
2. Weekly excitability tests using the Hilger facial nerve stimulator (WR Medical Electronics Co, St. Paul) were performed, stimulating the facial nerve trunk until full recovery was reached, or up to six months following the onset of the palsy.
3. Lacrimation and taste tests, audiogram (pure tone, speech and MCL [most comfortable level] tests), minimal cold caloric test, mastoid and internal auditory canal x-ray films and electromyography.
4. Blood analysis: peripheral blood count and differential count, glucose, urea, uric acid, VDRL test, proteins and gammaglobulins, cholesterol and heterophile antibody test.
5. Antiviral antibody titers determined by the complement fixation and indirect fluorescence tests against herpes simplex and zoster, Epstein-Barr virus, cytomegalic virus, mumps, adenovirus and influenza viruses. Two blood samples were taken from every patient at the clinical onset of the paralysis and 3-4 weeks later.
6. Immunological studies: quanitative serum IgG and IgM, complement (C_3 and C_4). Enumeration of B and T lymphocytes in the peripheral blood by determination of surface membrane IgM and E-rosette formation respectively.[13,14] The immunological studies were performed three times at 3-4 week intervals.

None of the patients received either medical or surgical therapy. All patients were examined and evaluated by one person (AA).

Statistical evaluation of the significance of the immunological changes was done by the Student *t* test.

RESULTS

Clinical. Among the 30 BP patients examined during the study period only 25 were available for follow-up studies.

The youngest patient was 3 years old and the oldest 78 years, with a mean age of 35 years. There was no significant difference between the sexes or affected side of paralysis.

Complete facial paralysis was found in 64% of the patients, while only 36% had incomplete paralysis. Table 1 summarizes the clinical manifestations and outcome of these two groups. Among the patients with incomplete paralysis the mandibular

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TABLE 1. CLINICAL MANIFESTATIONS AND OUTCOME OF BP PATIENTS (N = 25)

Clinical Manifestations and Outcome	*Complete Paralysis (N = 16)* No.	%	*Incomplete Paralysis (N = 9)* No.	%
Decreased or increased lacrimation on the involved side	10	62.5	4	44.4
Taste impairment of ant. 2/3 of tongue	2	12.5	5	55.5
Involvement of other cranial nerves	10	62.5	5	55.5
Complete recovery	11	68.7	8	88.8
Incomplete recovery	5	31.3	1	11.2

branch was most frequently involved. Of 5 patients with controlled diabetes mellitus 4 had complete palsy and 1 patient had an incomplete palsy.

Sensory cranial nerve involvement was found in 15 patients (60%). The most common nerve involved was the trigeminal or one of its branches (13 patients), followed by the eighth nerve (4 patients with cochlear and 1 with vestibular involvement) and the sensory branch of the vagus nerve (1 patient). The cochlear damage was expressed by subjective dysacusis. The audiometric examination revealed lateralization of the Weber test to the affected ear and unchanged threshold for pure tone sounds. Complete recovery of the sensory cranial nerves, which preceded the improvement of the facial nerve activity, was the rule.

The overall rate of complete recovery during a 6-month period of follow-up was 76%. Among the 6 patients who did not recover, 2 (8%) developed complete denervation of the facial nerve and the other 4 patients (16%) had incomplete recovery of different degrees. The complete clinical recovery of the facial nerve occurred mostly between 3-7 weeks after the clinical onset of the paralysis.

Virological. No significant serum antiviral antibody titer elevation of all seven viruses studied was found in the 25 BP patients examined.

Immunological. The serum immunoglobulins C_3 and C_4 obtained in the first visit were normal. The peripheral blood T and B lymphocytes were examined at 0-24, 25-60 and 61-100 days after the onset of the paralysis. Thirteen out of the 25 BP patients demonstrated changes in the T and B cell percentages, while the total amounts of peripheral blood lymphocytes were normal. The readings of the other 12 patients were normal (Table 2).

There was a significant increase ($p<0.001$) in the percentage of B cells in the initial period of the disease (0-24 days) as compared to the normal group (Fig 1). This increase returned slowly to normal levels, being still high ($p<0.05$) during the second period (25-60 days), and only in the late period (61-100 days) complete return to normal levels occurred. Among the 13 patients who had B cell changes a significant difference ($p<0.02$) between the first and the third periods was found.

The percentage of the T lymphocytes in the peripheral blood followed the same pattern as the B lymphocytes but in an opposite direction (Fig 2). There was a significant decrease in the first period (0-24 days) as compared to the normal group ($p<0.001$). During the second period (25-60 days) there was still a significant difference ($p<0.05$), while only in the third period (61-100 days) the T lymphocytes returned to normal values. There was a significant difference between the first and the third periods ($p<0.01$).

No correlation was found between the B and T lymphocyte alterations and the degree of paralysis, the recovery rate and the patient's age or sex.

DISCUSSION

In the present study the peripheral blood T and B lymphocyte subpopulations as well as the levels of IgG and IgM and C_3 and C_4 in the serum of BP patients were determined. A significant increase in the percentage of B lymphocytes and a significant decrease in the percentage of T lymphocytes in 13 of the patients (52%) were found, without changes in the total number of peripheral blood lymphocytes. These changes returned gradually to normal levels 60-100 days after the clinical onset of the disease. The lack of correlation between these results and the degree of paralysis and recovery rate indicates that the extent of nerve damage is not influenced by these immunological changes.

A decrease in peripheral blood T lymphocytes was found in several viral diseases, excluding infectious mononucleosis.[15-18] Experimentally it was found that human infection with influenza virus causes a significant reduction in the absolute number and percentage of T lymphocytes detected as early as 24 hours after inoculation.[19] A similar finding was found in a case of herpes zoster infection.[20] Herpes genitalis also caused a significant decrease in

TABLE 2. MEAN VALUES OF IgM-BEARING CELLS (B CELLS) AND E-ROSETTE-FORMING CELLS (T CELLS) IN THE NORMAL GROUP AND THE GROUP WHICH DEMONSTRATED B AND T CELL CHANGES*

		Examination Postparalysis *0-24 Days*	*25-60 Days*	*61-100 Days*
T cells	Abnormal (13)	62.1 ± 10.1%	75.5 ± 8.4%	82.5 ± 3.7%
	Normal (12)	82.6 ± 3.9%	83.3 ± 3.7%	81.6 ± 3.8%
B cells	Abnormal (13)	19.0 ± 2.4%	17.7 ± 4.2%	13.7 ± 4.0%
	Normal (12)	11.0 ± 1.3%	11.4 ± 6.3%	11.5 ± 3.4%

*Normal range: B cells - 12% ± 2; T cells - 85% ± 5.

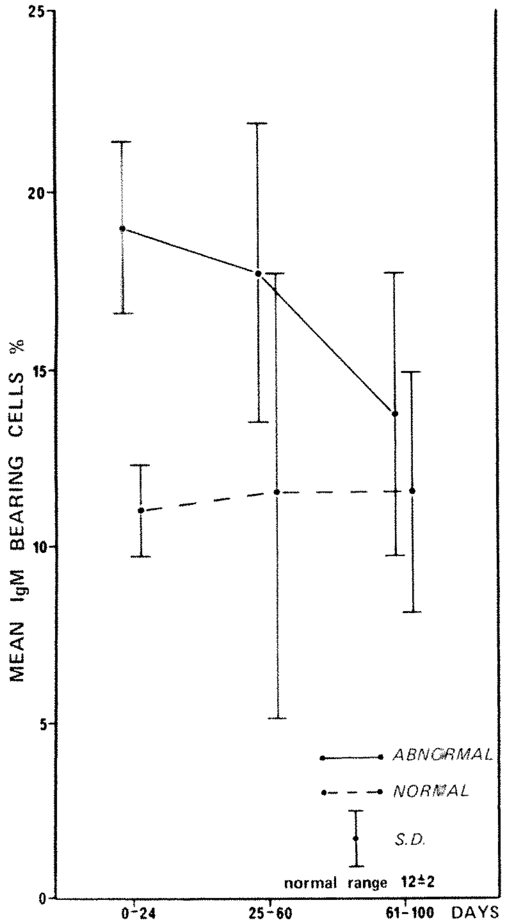

Fig 1. Changes in IgM-bearing cells (B lymphocytes) between the normal and abnormal groups during follow-up.

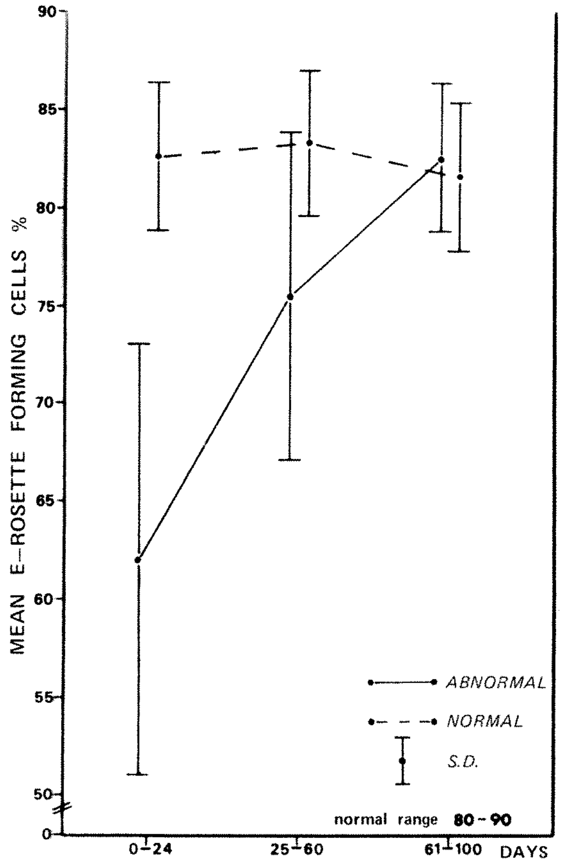

Fig 2. Changes in E-rosette forming cells (T lymphocytes) between the normal and abnormal groups during follow-up.

the percentage of "active" T lymphocytes, whereas the percentage of B lymphocytes remained normal.[21]

Most suggestive is the fact that similar changes in peripheral blood lymphocyte subpopulations, namely a decrease in T lymphocytes and sometimes an increase in B lymphocytes, were described also during the course of several demyelinating diseases, such as in acute exacerbations of multiple sclerosis (MS) and during the acute stage of Guillain-Barre syndrome (GBS).[22-25] The T lymphocyte depression in GBS was transient with a slow return to normal values during the first 4-6 weeks of the disease.[25] Similar immunological changes were not found in patients with other neurological diseases, thus raising the possibility that these changes may be of importance in the pathogeneses of GBS and MS and are not secondary to lesions of the nerve tissue.[24]

Bell's palsy, like GBS, is an acute demyelinating disease of the peripheral nervous system. In a histopathological study of a case of BP of 17 days' duration scattered degeneration of myelin sheaths and axons with a moderate increase of phagocytic cells were found in 10-30% of the facial nerve fibers. The perivascular area showed inflammatory reaction with petechiae.[26] Acute inflammatory reaction with lymphocytic infiltration and phagocytosis of myelin by macrophages was found also by Proctor et al in a BP patient who died 13 days after the clinical onset of the disease. According to these findings it was suggested that the inflammatory lesions observed in the facial nerve may be caused by a viral infection.[1] Experimentally it was demonstrated that inoculation of herpes simplex virus in rabbits through the stylomastoid foramen produced facial paralysis with the histopathological pattern of inflammation and demyelination.[2] This virus was found to infect the neurons in the geniculate ganglia of newborn hamsters.[3] Viruses may cause other human and experimental demyelinating disease as well.[7,8,10] The histopathological pattern of nerve damage indicates a surprising similarity between the findings observed in BP and those in GBS.[27] In both diseases an inflammatory demyelination neuritis was found, marked by lymphocytic infiltrate. The clinical, immunological and histopathological similarities between BP and GBS may indicate that both diseases may share a similar etiology and pathogenesis.

Abramski et al found that peripheral blood lymphocytes from BP patients showed significant transformation with the presence of human basic protein of peripheral nerve myelin.[12] The experimental study of McGovern et al on hyperimmune dogs supplied additional support to the immunological concept of BP. These dogs developed greater facial paralysis and suffered more intense nerve damage than nonsensitized dogs after injection of vasoconstrictors within the facial nerve canal.[11,28]

Our clinical observations are in agreement with those of other studies. The involvement of other sensory cranial nerves, which was found in 60% of our patients, supports the concept that BP is not an isolated disease of the facial nerve, but is rather a cranial polyneuropathy.[4-6] This phenomenon indicates an involvement of a systemic cause, such as a virus, which for some unknown reason attacks the cranial nerves.

The viral theory is supported by clinical observations[29,30] and serological investigations.[31-33] In the present study the antibody titers of seven different viruses were investigated but no significant changes were found. Similar results were reported also by others who failed to demonstrate a viral infection, neither by isolation of a virus nor by changes in antibody titers.[34-37] Vahlne et al found a higher prevalence of high antibody titers to herpes simplex in the BP patients as compared to the control group, both with complement fixation test and radioimmunoassay.[38] The controversial findings led some investigators to suggest that BP is caused by reactivation of a latent herpes simplex virus.[6,33,38] However, in an experimental study it was demonstrated that serum-neutralizing antibodies are not needed to maintain the latent state of herpes virus infection, but whenever reactivation occurs it is followed with an increase in antibody titers.[39] Nevertheless, the role of a viral infection in the pathogenesis of BP cannot be denied.

Recently we studied the interferon (IFN) system in BP and found that 72% of 32 patients demonstrated a high serum IFN level or an antiviral state of their peripheral blood mononuclear cells.[40] Studies on the IFN system in viral diseases demonstrated similar results.[41]

In conclusion, the clinical, histopathological and immunological resemblance between BP and GBS indicate that BP belongs to the group of acute demyelinating diseases of the peripheral nervous system. The cranial polyneuropathy and the serological and viral studies, although not conclusive, suggest that an acute viral infection or reactivation of a latent virus may be the etiologic cause of BP. A viral infection may induce T and B cell changes on the one hand, and on the other hand may set up an autoimmune reaction against components of the peripheral nerve myelin leading to demyelination of cranial nerves, especially the facial nerve, in a way not yet clear. Whether the changes in the T and B lymphocyte subpopulations are significant or not in the pathogenesis of BP waits for further clarification. This study brings evidence that systemic changes occur in BP and that these changes affect the immune system.

REFERENCES

1. Proctor B, Corgill DA, Proud G. The pathology of Bell's palsy. Trans Am Acad Ophthalmol Otolaryngol 1976; 82:70-80.

2. Kumagami H. Experimental facial nerve paralysis. Arch Otolaryngol 1972; 95:305-12.

3. Davis LE. Experimental viral infections of the facial nerve and geniculate ganglion. Ann Neurol 1981; 9:120-5.

4. Djupesland G, Degre M, Stien R, Skrede S. Acute peripheral facial palsy. Part of a cranial polyneuropathy? Arch Otolaryngol 1977; 103:641-4.

5. May M, Hardin WB. Facial palsy: interpretation of neurologic findings. Trans Am Acad Ophthalmol Otolaryngol 1977; 84(ORL):710-22.

6. Adour KK, Byl FM, Hilsinger RL, et al. The true nature of Bell's palsy: analysis of 1000 consecutive patients. Laryngoscope 1978; 88:787-800.

7. Weiner LP, Johnson RT, Herndon RM. Viral infections and demyelinating diseases. N Engl J Med 1973; 288:1103-9.

8. Cook SD, Dowling PC. Multiple sclerosis and viruses: an overview. Neurology 1980; 30:80-91.

9. Cook SD, Dowling PC. The role of autoantibody and immune complexes in the pathogenesis of Guillain-Barre syndrome. Ann Neurol 1981; 9 Suppl:70-9.

10. Lampert PW. Autoimmune and virus-induced demyelinating diseases. Am J Pathol 1978; 91: 176-208.

11. McGovern FH, Estevez J. The concept of Bell's palsy as an immunologically mediated disease. In: Shambaugh GE, Shea JJ, eds. Proceedings of the Shambaugh Fifth International Workshop on Middle Ear Microsurgery and Fluctuant Hearing Loss. Huntsville, Ala: The Strode Publishers, 1976:229-32.

12. Abramski O, Webb C, Teitelbaum D, Arnon R. Cellular immune response to peripheral nerve basic protein in idiopathic facial paralysis (Bell's palsy). J Neurol Sci 1975; 26:13-20.

13. Bentwich Z, Kunkel HG. Specific properties of human B and T lymphocytes and alterations in disease. Transplant Rev 1973; 16:29-50.

14. Hofman F, Cohen A, Zipori D, et al. Binding of F(ab')₂ of normal human IgG to human lymphocytes. J Immunol 1977; 119:2209-11.

15. Wybran J, Fudenberg HH. Thymus-derived rosette-forming cells in various human disease states: cancer, lymphoma, bacterial and viral infections, and other diseases. J Clin Invest 1973; 52:1026-32.

16. Rowlands DT, Daniele RP. Lymphocyte subpopulations in human disease. Human Pathol 1977; 8:117-20.

17. Mangi RJ, Dwyer JM, Nuderman JD, Kantor FS. Decreased circulating T cells during viral pharyngitis. Ann Intern Med 1974; 81:557-8.

18. Utsinger PD. Lymphocyte changes in viral infections. Ann Intern Med 1975; 83:82.

19. Scheinberg MA, Blacklow NR, Goldstein AL, et al. Influenza: response of T-cell lymphopenia to thymosin. N Engl J Med 1976; 294:1208-11.

20. Russo L, Russo AM, Viola M, Russo PV. T-cell lymphopenia in viral infection. N Engl J Med 1976; 295:623.

21. Ishiguro T, Ozaski Y, Yokoyama MM, Tseng CH, Chao W. Peripheral lymphocytes subpopulations in patients with herpes genitalis. Immunobiology 1980; 157:24-9.

22. Lisak RP, Levinson AI, Zweiman B, Abdou NI. T and B lymphocytes in multiple sclerosis. Clin Exp Immunol 1975; 22: 30-4.

23. Sagar HJ, Alonby ID. Lymphocyte subpopulations in multiple sclerosis. J Neurol Sci 1979; 43:133-48.

24. Nyland H, Naess A. T-lymphocytes in peripheral blood from patients with neurological diseases. Acta Neurol Scand 1978; 58:272-9.

25. Nyland H, Naess A. Lymphocyte subpopulations in blood and CSF from patients with acute Guillain-Barre syndrome. Eur Neurol 1978; 17:247-52.

26. Reddy JB, Liu J, Balski S, Fisher J. Histopathology of Bell's palsy. Eye Ear Nose Throat Month 1966; 45:62-5.

27. Asbury AK, Arnason BGW, Adams RD. The inflammatory lesion in idiopathic polyneuritis. Medicine 1969; 48:173-215.

28. McGovern FH, Edgemon LJ, Konigsmark BW. Experimental ischemic facial paralysis. Arch Otolaryngol 1972; 95: 331-4.

29. Leibowitz U. Epidemic incidence of Bell's palsy. Brain 1969; 92:109-14.

30. Korczyn AD, Swirski R, Henig E. Bell's palsy and viral infections. Eur Neurol 1973; 10:191-6.

31. Tomita H, Hayakawa W, Honda R. Varicella-zoster virus in idiopathic facial palsy. Arch Otolaryngol 1972; 95:364-8.

32. Adour KK, Bell DN, Hilsinger RL. Herpes simplex virus in idiopathic facial paralysis (Bell's palsy). JAMA 1975; 233:527-30.

33. Djupesland G, Berdal P, Johannessen TA, et al. Viral infection as a cause of acute peripheral facial palsy. Arch Otolaryngol 1975; 102:403-6.

34. Dalton GA. Bell's palsy: some problems of prognosis and treatment. Br Med J 1960; 1:1765-70.

35. Dodge PR, Poskanzer DC. Varicella zoster and herpes simplex antibody responses in patients with Bell's palsy. Neurology 1962; 12:34-5.

36. McCormick D. Herpes simplex virus as a cause of Bell's palsy. Lancet 1972; 1:937-9.

37. Brackman DE. Bell's palsy: incidence, etiology and results of medical treatment. Otolaryngol Clin North Am 1974; 7:357-68.

38. Vahlne A, Edström S, Arstila P, et al. Bell's palsy and herpes simplex virus. Arch Otolaryngol 1981; 107:79-81.

39. Sekizawa T, Openshaw H, Wohlenberg C, Notkins AL. Latency of herpes simplex virus in absence of neutralizing antibody: model for reactivation. Science 1980; 210:1026-8.

40. Aviel A, Hahn T, Ostfeld E, Bregman V, Marshak G. Interferon antiviral system in Bell's palsy. Acta Otolaryngol (Stockh) 1981; 91:69-73.

41. Levin S, Hahn T. Evaluation of the human interferon system in viral disease. J Clin Exp Immunol 1981; 46:475-83.

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THE 16TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEAD AND NECK RADIOLOGY

The 16th Annual Meeting of the American Society of Head and Neck Radiology will be held May 26-29, 1983, at the Boston Marriott Hotel. Inquiries should be directed to Barbara Carter, MD, North East Medical Center, 171 Harrison Avenue, Boston, MA 02111.

Ann Otol Rhinol Laryngol 92:1983

CARCINOMA OF THE PANCREAS PRESENTING WITH BILATERAL TONSILLAR METASTASES

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A 59-year-old woman presented with bilateral tonsillar masses due to metastases from a primary pancreatic carcinoma. Tonsillar metastases from many different primary tumors are well documented in the literature, but this seems to be the first case in which the pancreas was the primary site. It is also one of the very few recorded cases in which the patient's presenting symptoms were due to tonsillar metastases.

Metastatic tumors are rare in the tonsils and are not mentioned in standard textbooks of pathology. Brownson et al[1] were able to find reports of 76 cases of metastatic carcinoma of the tonsils in the literature up to 1979 but only 51 of them were sufficiently detailed to allow analysis. In the majority of cases the tonsillar metastases became manifest after the diagnosis of the primary tumor. In this paper, we describe a patient with pancreatic carcinoma in whom the presenting clinical symptoms were due to bilateral tonsillar metastases. As far as we are aware, this is the first report of metastases to the tonsils from a primary pancreatic tumor.

CASE REPORT

A 59-year-old woman was referred to the ENT department with a sore throat of one month's duration which had not responded to treatment with penicillin. Examination revealed a blood pressure of 100/60 mm Hg, pulse rate of 86/min and a temperature of 37.8°C. There were no abnormal findings upon examination of the chest, abdomen or nervous system. Both pharyngeal tonsils were enlarged, ulcerated and covered by a fibrinous exudate. A mobile lymph node, 3 cm in diameter, was present in the left posterior triangle of the neck and similar, but smaller, nodes were present along both jugular veins.

Clinical blood examinations yielded the following results: hemoglobin, 9.1 g/100 ml; erythrocytes, 3.2 million/cu mm; leukocytes, 21,500/cu mm; the differential count was normal. Results of blood chemistry and urine studies were normal. No pathogenic organisms were cultured from tonsillar swabs. X-ray films of the chest revealed a polycyclic mass at the apex of the left lung and a left pleural effusion.

Biopsies of the tonsils and the posterior triangle lymph node showed infiltration by a poorly differentiated malignant tumor containing numerous bizarre tumor giant cells (Fig. 1).

During the second week after admission the patient began to complain of pain in the left upper quadrant of the abdomen, accompanied by constipation. An irregular nontender mass could be felt on deep palpation in the left midabdomen. Intravenous pyelography and barium enema test results were normal. Malignant cells were seen on cytological examination of ascitic and left pleural fluids.

The patient's course was rapidly downhill. The abdominal mass increased rapidly in size and the patient became jaundiced. Laboratory tests yielded the following values: serum bilirubin, total, 5.8 mg/100 ml; direct, 3.5 mg/100 ml; and indirect, 2.3 mg/100 ml; SGOT, 230 IU/1; SGPT, 180 IU/1; serum protein, 5.9 g/100 ml; serum alkaline phosphatase, 10 Bessay-Lowry units/100 ml. Fine needle biopsy of the left apical lung tumor revealed undifferentiated large cell carcinoma. Percutaneous transhepatic cholangiography showed obstruction of the lower end of the common bile duct, compatible with carcinoma of the head of the pancreas.

The patient developed dyspnea and marked edema of the lower limbs. She became comatose and died three weeks after admission.

Postmortem Findings. External examination revealed severe generalized edema, jaundice of the skin and sclera, and marked abdominal distension. The peritoneal cavity contained 2,800 ml of clear yellow fluid. Similar but smaller effusions were present in both pleural cavities.

Both tonsils were replaced by firm grey-white tumor tissue and a small nodule of similar tissue was present in the left pyriform fossa. A rounded, well-demarcated, firm, whitish tumor mass, 9x10 cm, was present in the upper lobe of the left lung. The large bronchi were normal. The hilar lymph nodes were anthracotic but free of tumor.

A large tumor mass, 20 cm in diameter, involved the head and body of the pancreas and peripancreatic lymph nodes. It invaded the duodenal wall 6 cm distal to the ampulla of Vater, and also infiltrated the lower third of the common bile duct. The splenic vein was invaded and its lumen occupied by tumor thrombus. The portal vein was not involved and there were no metatases in the liver.

Both adrenal glands were enlarged and almost completely replaced by grey-white tumor tissue.

Histological Examination. The tumor masses in the left lung, pancreas, tonsils, abdominal lymph nodes, left pyriform fossa and adrenal glands showed a similar histological picture. The predominant cells were large, rounded, or polyhedral cells with abundant cytoplasm and large vesicular nuclei. They were arranged in loose sheets with no evidence of gland formation (Fig. 2). Numerous pleomorphic giant cells with bizarre single or multiple nuclei were present. Mitotic figures were abundant. In many fields there were scattered spindle-shaped cells and occasionally these were so numerous as to result in a sarcomatous appearance (Fig. 3). There were multiple areas of necrosis in the tonsillar and pancreatic masses. The tumor in the lung was well circumscribed and partly separated from the surrounding atelectatic lung parenchyma by a fibrous capsule (Fig. 4). Stains for mucin were negative. The thoracic lymph nodes were not involved.

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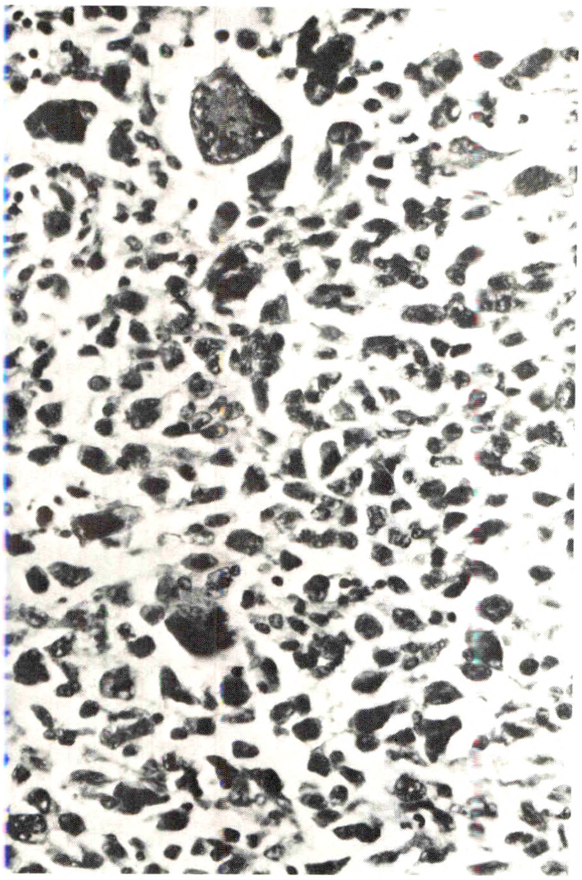

Fig. 1. Biopsy of tonsil showing poorly differentiated tumor with multinucleated tumor giant cells. (H & E, x400)

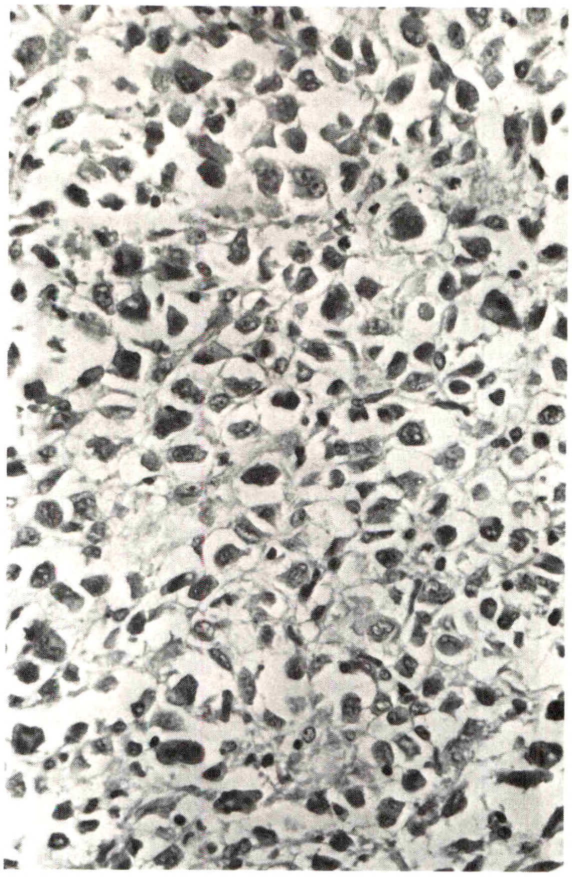

Fig. 2. Pancreatic tumor showing loosely arranged rounded or polyhedral cells with abundant cytoplasm and prominent nuclei. (H & E, x250)

DISCUSSION

The histological features of the tonsillar, pulmonary and pancreatic tumors in our patient were similar and it is unlikely that they represent more than one independent primary tumor. Of the three, the tonsil seems the least likely site of the primary tumor. Bilateral primary carcinoma of the tonsil is extremely rare and the histological picture was unlike that of the usual primary tonsillar cancer.

The decision as to whether the primary tumor was in the pancreas or lung is more difficult. The histological features are consistent with a giant cell carcinoma of the lung[2] or with the pleomorphic large cell type of pancreatic carcinoma.[3] The fact that the lung tumor presented as a well-circumscribed rounded mass without involvement of the bronchial tree or hilar lymph nodes is more suggestive of a metastasis than of a primary lung cancer. On the other hand, the presence of a large pancreatic mass with direct infiltration of surrounding structures and peripancreatic lymph nodes favors a primary pancreatic tumor. It is well known that the clinical and radiological findings of metastatic pancreatic carcinoma may simulate primary carcinoma of the lung.[4-6] In 3.4% of a recent large series of patients with pancreatic carcinoma, the initial diagnosis was primary bronchogenic carcinoma.[5] We believe that the macroscopic and histological findings in our patient favor the view that the tonsillar and lung tumors were metastases from a primary carcinoma of the pancreas.

Spread of pancreatic carcinoma to the lungs and tonsils can occur by either vascular or lymphatic channels. Lymphatic metastases to the hilar or tracheobronchial lymph nodes with secondary invasion of large bronchi is a well-recognized phenomenon in pancreatic carcinoma.[5] There was, however, no evidence of this in our case and hematogenous spread seems to be a more likely explanation of the lung metastases. Hematogenous dissemination to the lungs without involvement of the liver can be explained by lymphatic spread via the lumbar-collecting trunks to the thoracic duct.[7] Hematogenous spread also seems to be the most likely explanation of the tonsillar metastases, probably via the systemic arterial circulation or possibly via the paravertebral plexus of Batson. Retrograde lymphatic spread to the tonsils is thought to be a much less likely pathway for tonsillar metastases, particularly since the cervical lymph nodes are usually uninvolved.[1] The presence of a tumor nodule in the left pyriform fossa in our patient is of interest in view of a recent report of metastasis to the epiglottis[8] in a patient with pancreatic carcinoma.

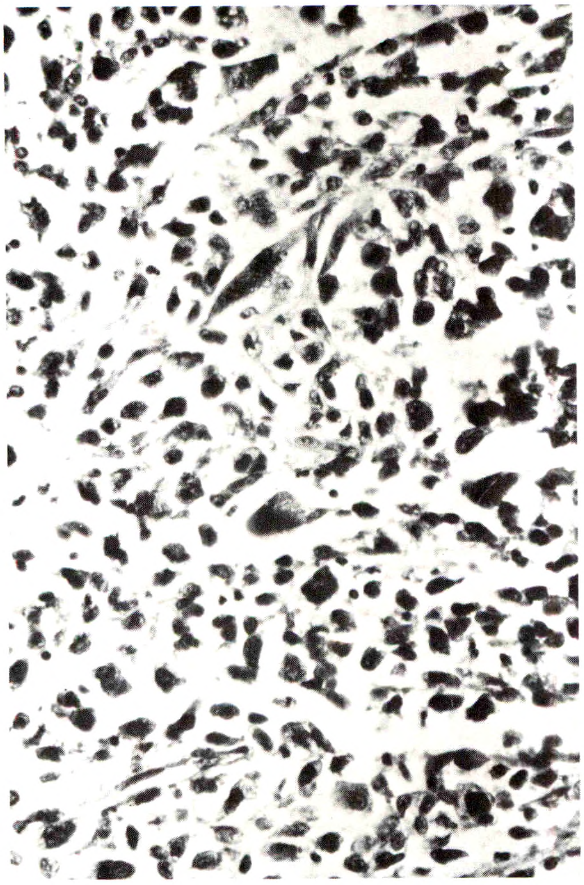

Fig. 3. Pancreatic tumor showing marked cellular pleomorphism, tumor giant cells, and elongated spindle-shaped cells, giving pseudosarcomatous pattern. (H & E, x400)

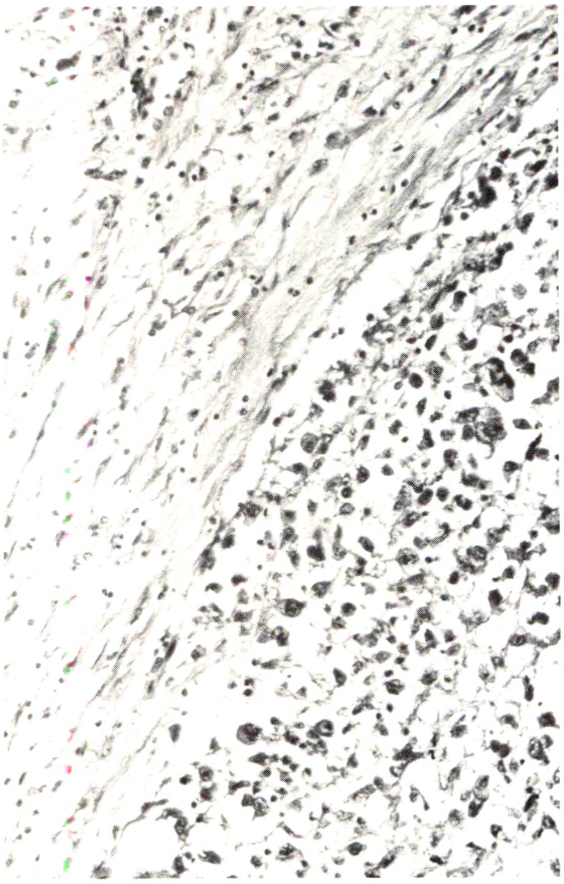

Fig. 4. Well-demarcated tumor mass in left lung showing similar histological features to tonsillar and pancreatic tumors. (H & E, x100)

Extratonsillar primary tumors rarely metastasize to the tonsil. Sellars[9] was able to find 20 case reports of metastatic tumors of the tonsil in the literature between 1858 and 1968. By 1979, Brownson et al[1] found reports of 76 cases in the literature, but in many of these, detailed clinical or pathological data were lacking.

The most common tumors to give rise to tonsillar metastases have been malignant melanoma, carcinomas of the breast and lung, hypernephroma, seminoma and carcinoma of the stomach.[1] In addition, there are isolated reports of tonsillar metastases in carcinoma of the prostate, rectum or pyriform sinus,[1] neuroepithelioma,[10] Wilms tumor[10] and choriocarcinoma.[11] Ashur et al[12] have recently reported an additional case of metastatic malignant melanoma in the tonsil. Pancreatic carcinoma is not mentioned as the source of tonsillar metastases in the reviews of Sellars[9] or Brownson,[1] but the latter author refers briefly to two cases of tonsillar metastases from tumors in the gallbladder-common bile duct area.

Metastases to the tonsils are more often unilateral than bilateral. Bilateral tonsillar metastases are, however, well documented and are, in fact, more frequent than unilateral metastases in cases of melanoma, seminoma and carcinoma of the breast or stomach.[1]

The time interval between the diagnosis of the primary tumor and the appearance of tonsillar metastases is usually less than one year but may be much longer in cases of breast carcinoma, hypernephroma and malignant melanoma. Our case was unusual in that the patient's presenting symptoms were due to the tonsillar metastases. As far as we are aware, this has been previously described only in cases of hypernephroma.[1]

The rapid clinical course in our patient is consistent with the short mean survival time reported for patients with tonsillar metastases, regardless of the nature or site of the primary tumor.[1]

REFERENCES

1. Brownson RJ, Jaques WG, LaMonte SE, Zollinger WK. Hypernephroma metastatic to the palatine tonsils. Ann Otol Rhinol Laryngol 1979; 88:235-40.

2. Carter D, Eggleston JC. Tumors of the lower respiratory tract. Armed Forces Institute of Pathology, second series fascicle 17, 1979.

3. Alguacil Garcia A, Weiland LH. The histologic spectrum, prognosis and histogenesis of the sarcomatoid carcinoma of the pancreas. Cancer 1977; 39:1181-9.

4. Lisa JR, Trinidad S, Rosenblatt MB. Pulmonary manifestations of carcinoma of the pancreas. Cancer 1964; 17:395-401.

5. Cassiere SG, McLain DA, Emory WB, Hatch HB. Metastatic carcinoma of the pancreas simulating primary bronchogenic carcinoma. Cancer 1980; 46:2319-21.

6. Rosenblatt MB, Lisa JR, Trinidad S. Pitfalls in the clinical and histological diagnosis of bronchogenic carcinoma. Dis Chest 1966; 49:396-404.

7. Cubilla AL, Fitzgerald PJ. Classification of pancreatic cancer (nonendocrine). Mayo Clin Proc 1979; 54:449-58.

8. Oku T, Hasegawa M, Watanabe I, Nasu M, Aoki N. Pancreatic cancer with metastasis to the larynx. J Laryngol Otol 1980; 94:1205-9.

9. Sellars SL. Metastatic tumors of the tonsils. J Laryngol Otol 1971; 85:289-91.

10. Hyams VJ. Differential diagnosis of neoplasia of the palatine tonsil. Clin Otolaryngol 1978; 3:117-26.

11. Kutty MK, Shenoy AV. Metastatic choriocarcinoma of the tonsil following hysterectomy for an invasive mole and a period of "inactivity" of trophoblastic tissue: report of a case. Oral Surg 1971; 32:248-52.

12. Ashur H, Mizrachi S, Ben Hur N, Odberg L. Metastatic malignant melanoma to the palatine tonsils: report of a case. J Oral Surg 1979; 37:110-2.

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POSTGRADUATE COURSE IN BASIC REVIEW AND RECENT ADVANCES IN NEURORADIOLOGY AND HEAD AND NECK RADIOLOGY

A postgraduate course in basic review and recent advances in neuroradiology and head and neck radiology will be held at the Copley Plaza Hotel in Boston, Massachusetts, on September 26-30, 1983. The program chairman is Juan M. Taveras, MD, and the program directors are Kenneth R. Davis, MD, and Alfred L. Weber, MD. For further information contact Harvard Medical School, Department of Continuing Education, Boston, MA 02115 (617) 732-1525.

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EFFECTS OF COLD AIR AND EXERCISE ON NASAL PATENCY

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Changes in nasal patency were examined in six warmly clad, healthy adult subjects at rest and with exercise in a cold chamber at 0°C by computer-aided respiratory rhinometry. In all subjects change from comfortable laboratory conditions to the cold chamber was accompanied by a decrease in nasal patency. Subjects remained in the chamber where this response was reversed by exercise in each case.

INTRODUCTION

Nasal mucosal responses in subjects both at rest and with exercise in a cold environment are described in this communication. An investigation of the combined effects of cold and exercise has not been reported hitherto.

Decrease in nasal patency of resting subjects breathing cold air has been demonstrated quantitatively by Takagi et al[1] and by Salman et al.[2] Drettner[3] has given an account of his own rhinoscopic findings and those of other observers but the appearances which were found on cold exposure do not compose a clear picture of mucosal behavior.

Increase in nasal patency with exercise is well recognized by clinicians and has been investigated by Richerson and Seebohm,[4] Baumann and Masing,[5] and Masing et al,[6] Dallimore and Eccles,[7] Hasegawa and Kern[8] and by Saketkhoo et al.[9] In an earlier paper we reported having found little change in nasal patency of subjects when measurements were made before and after a brisk walk in subfreezing conditions.[10]

These latter observations were made in subjects who experienced a combination of cold exposure and exercise. The effects of both exposure and exercise in a cold environment have now been examined under controlled conditions and the results are reported.

METHODS

Results were obtained from six healthy adult volunteer subjects. A posterior rhinometric technique was employed using a scuba mask with a pneumotach (Fleish No. 2) in the faceplate; transnasal pressure and flow were sensed by transducers (Validyne MP-45). The amplified signals were led via a buffered interface to an analog-to-digital converter where they were sampled every 20 ms. The values thus obtained by discontinuous sampling and digitization were stored in the memory of a microprocessor (Imsai 8080A) which was programmed to compute and produce an on-line readout and printout of minute ventilation, average transnasal pressure and resistance on completion of each series of five consecutive breaths.[11-13]

Maximum physical working capacity (PWC$_{max}$) was determined for each subject.[14] At a separate session, nasal resistance measurements were obtained from subjects at rest in a comfortable environment (24°C, 50% relative humidity).

Resting. Each subject was then warmly dressed and seated on a cycle ergometer in a cold chamber at 0°C. Measurements of minute ventilation, average transnasal pressure and nasal resistance were made at five-minute intervals throughout the duration of each experiment.

Exercising. When nasal resistance stabilized the subjects remained in the cold chamber and began to exercise at 50% PWC$_{max}$. Two subjects exercised at this level for five to ten minutes only; the remaining four continued for 20-30 minutes and their exercise level was then increased to 75% PWC$_{max}$ for a further five to ten minutes.

Recovery. Three subjects were exposed at rest in the chamber for 20 minutes and their nasal resistance was measured at intervals following return to comfortable laboratory conditions, ie, during spontaneous recovery and following application of 0.1% xylometazoline nasal spray.

Posttreatment Exposure. One subject was exposed in the chamber after application of 0.1% xylometazoline spray.

Subjects blew their noses before measurements were made in order to avoid obstruction of the nasal passages by accumulated mucus secretion.

RESULTS

Resistance values demonstrate a decrease in nasal patency on cold exposure which is reversed by exercise in the continued presence of the cold stimulus. The magnitude of the exercise response is directly related to severity of exercise. No responses were found in a xylometazoline-decongested nose (Table).

Resting. All six subjects showed a decrease in nasal patency which approached a plateau after 20 minutes of cold exposure.

Exercising. All six exposed subjects showed an increase in nasal patency with exercise within the cold chamber to approximate pre-exposure levels. In two subjects this occurred at 50% PWC$_{max}$. In four subjects the reduction of resistance at 50% PWC$_{max}$ was minimal but remained constant for as long as 30 minutes; when the level of exercise was increased to 75% PWC$_{max}$ a more marked reduction of resistance took place almost immediately.

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NASAL RESISTANCE WITH COLD EXPOSURE AND EXERCISE

	Nasal Resistance cm H_2O/liter/s			
	24°C 50% RH	*0°C 95% RH*		
		20-min	*Continued Exposure*	
Subject	*Pre-exposure, Resting*	*Exposure, Resting*	*50% PWC_{max}*	*75% PWC_{max}*
1*	3.5	5.2	3.5	3.0
2	2.8	4.5	4.5	2.2
3	2.3	3.9	1.8	—
4	2.2	3.6	3.4	2.8
5	2.8	4.1	2.1	—
6	2.4	4.8	4.4	2.8
1†	2.3	2.4		

RH - Relative humidity; PWC_{max} - Maximum physical working capacity.
*Patient has perennial rhinitis.
†With 0.1% xylometazoline.

Recovery. Recovery approaching pre-exposure levels of nasal resistance occurred 20-60 minutes after return to a comfortable environment. Reduction of resistance with xylometazoline was similar in rapidity to that induced by exercise (Figure).

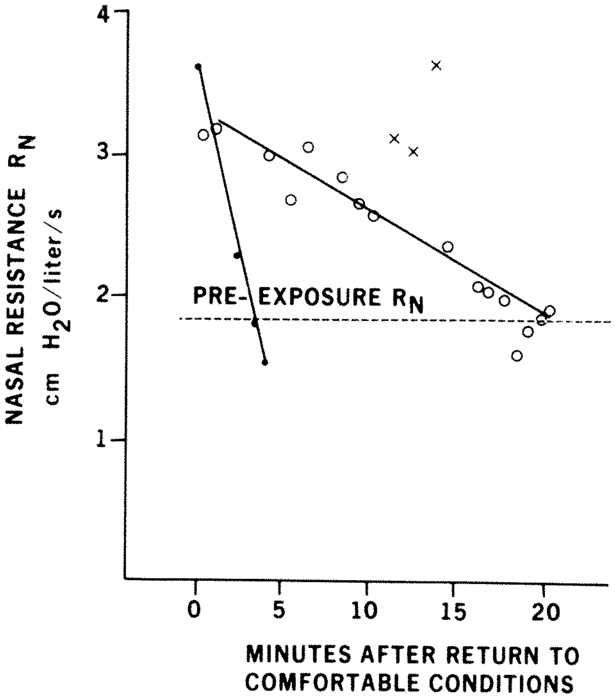
Posttreatment Exposure. The subject whose nasal mucosa was decongested by xylometazoline showed no change in nasal resistance on exposure to cold. Only two subjects demonstrated copious mucus secretion on nose blowing, but others were sometimes unaware of a mucus accumulation which was clearly demonstrated by resistance measurements before and after nose blowing (Figure).

The degree of nasal congestion on cold exposure, exercise and recovery showed quite large intersubject and intrasubject variations. Furthermore, some resting subjects after 20 minutes of cold exposure demonstrated continued increase in congestion for several minutes after return to a comfortable environment. There have been occasions when cold exposure induced no change and others when recovery extended beyond 60 minutes in the resting subject.

DISCUSSION

Results of experiments described in this communication confirm the observations of other workers[1, 2] that nasal resistance to respiratory airflow in human subjects at rest increases with exposure to cold air.

Extended time courses of about 20 minutes are required to achieve a resistive plateau on exposure to cold air and 20-60 minutes to recover or return to a comfortable environment in subjects at rest. Their duration typifies the sluggishness of a local metabolic response taking place in the nasal mucosa where the cold stimulus is concentrated in warmly dressed subjects. By contrast, the nasal decongestive response to exercise is much more rapid and characteristically in keeping with a localized nervous action.[4-9]



Recovery from cold-induced nasal resistance of a resting subject in comfortable room conditions. ○ - Spontaneous; ● - After local application of 0.1% xylometazoline; X - High resistance between 10 and 15 minutes due to accumulated mucus; previous trend of return to pre-exposure patency continues after nose-blowing at 15 minutes.

In all six subjects cold-induced nasal resistance reverted to pre-exposure values with exercise in the cold environment at 50%-75% PWC_{max}. The degree of decongestion was directly related to severity and independent of duration of exercise and appears somewhat less than that attained in a comfortable environment. Subjects who continued to exercise at 50% PWC_{max} for as long as 30 minutes maintained a constant level of nasal resistance and when exercise was increased to 75% PWC_{max} a further reduction in nasal resistance took place almost immediately.

Application of the nasal decongestant 0.1% xylometazoline blocked the congestive response to cold. By comparison, subjects who walked briskly from the comfortable laboratory into 0°C outdoor conditions did not demonstrate nasal congestion on their return to the laboratory after ten to 15 minutes of continued brisk walking in the cold;[10] in these cases exercise blocked the cold response. When xylometazoline was applied to nasal mucosa congested by cold exposure (Figure), rapid decongestion took place. The rapidity of decongestion (less than five minutes) which occurs with both exercise and xylometazoline suggests that the mucosal swelling is more likely vascular than edematous, and indeed it would be reasonable to expect that removal of tissue fluid in the presence of capillaries constricted by xylometazoline could be quite a lengthy process.

ACKNOWLEDGMENTS — The authors wish to thank Miss A. Au Yeung for invaluable secretarial help and the Ontario Thoracic Society for generous funding.

REFERENCES

1. Takagi Y, Proctor DF, Salman S, Evering S. Effects of cold air and carbon dioxide on nasal airflow resistance. Ann Otol Rhinol Laryngol 1969; 78:40-8.

2. Salman S, Proctor DF, Swift DL, Evering S. Nasal resistance: description of a method and effect of temperature and humidity changes. Ann Otol Rhinol Laryngol 1971; 80:736-43.

3. Drettner B. Vascular reactions of the human nasal mucosa on exposure to cold. Acta Otolaryngol (Stockh) 1961; Suppl 166.

4. Richerson HB, Seebohm PM. Nasal airway response to exercise. J Allergy 1968; 41:269-84.

5. Baumann A, Masing H. Über den EinfluB körperlicher Arbeit auf den Nasenwiderstand. Z Laryngol Rhinol Otol 1970; 49:264-70.

6. Masing H, Laacke R, Leykauf R. Nasal pressure flow studies in adults and children. Rhinology 1974; 12:137-43.

7. Dallimore NS, Eccles R. Changes in human nasal resistance associated with exercise, hyperventilation and rebreathing. Acta Otolaryngol (Stockh) 1977; 84:416-21.

8. Hasegawa M, Kern EB. The effect of breath holding, hyperventilation and exercise on nasal resistance. Rhinology 1978; 16:243-9.

9. Saketkhoo K, Kaplan I, Sackner MA. Effect of exercise on mucous velocity and nasal airflow resistance in normal subjects. J Appl Physiol 1979; 46:369-71.

10. Cole P, Fastag O, Forsyth R. Variability in nasal resistance measurements. J Otolaryngol 1980; 9:309-15.

11. Cole P, Niinimaa V, Mintz S, Silverman F. Work of nasal breathing: measurement of each nostril independently using a split mask. Acta Otolaryngol (Stockh) 1979; 88:148-54.

12. Cole P, Fastag O, Niinimaa V. Computer-aided rhinometry. Acta Otolaryngol (Stockh) 1980; 90:139-42.

13. Cole P. Respiratory rhinometry: a review of recent trends. Rhinology 1980; 18:3-8.

14. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. J Appl Physiol 1955; 7:218-21.

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ABNORMAL VENOUS DRAINAGE SIMULATING A GLOMUS JUGULARE TUMOR

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Knowledge of the arterial supply and the venous drainage of a glomus jugulare tumor is of most importance for surgery, and close cooperation between the neuroradiologist and the otolaryngologist is necessary. The possibility of a variation of the vascular anatomy should be kept in mind. We report a patient with a reddish mass behind the eardrum which was found to be her transverse sinus running in a vertical direction, ending in a sigmoid sinus which was passing close to the foramen magnum.

In a recent publication Deeb et al[1] called attention to a hazard in diagnosis of glomus jugulare tumors. He found a bluish mass in the hypotympanic space in a 25-year-old female to be a high positioned, blind-ending jugular bulb. Retrograde jugular venography had been interpreted as obstruction of the right sigmoid sinus at the level of the bulb. The aim of this communication is to present a case with a similar history and angiograms demonstrating an abnormal route, not an aplasia, of the sigmoid sinus.

CASE REPORT

A woman 40 years old was admitted to the ENT department with a pulsatile tinnitus in her right ear which she had had for more than 20 years. Ten years before admission she had been examined by an ENT specialist who found a bluish mass in the hypotympanic area of the middle ear. The patient had a normal cochlear function and only a small conductive hearing loss. Vestibular tests were all normal. On the suspicion of a glomus jugulare tumor an angiographic examination was performed in another hospital. No pathological changes were seen on the angiograms but subtraction technique was not used. The venograms were judged normal. It was therefore decided not to operate and to follow the patient closely.

Over the next ten years there was no change in the symptoms. The tinnitus was of the same pulsatile quality and of the same magnitude. The discrete conductive hearing loss was unchanged. No abnormal neurological signs were observed. In spite

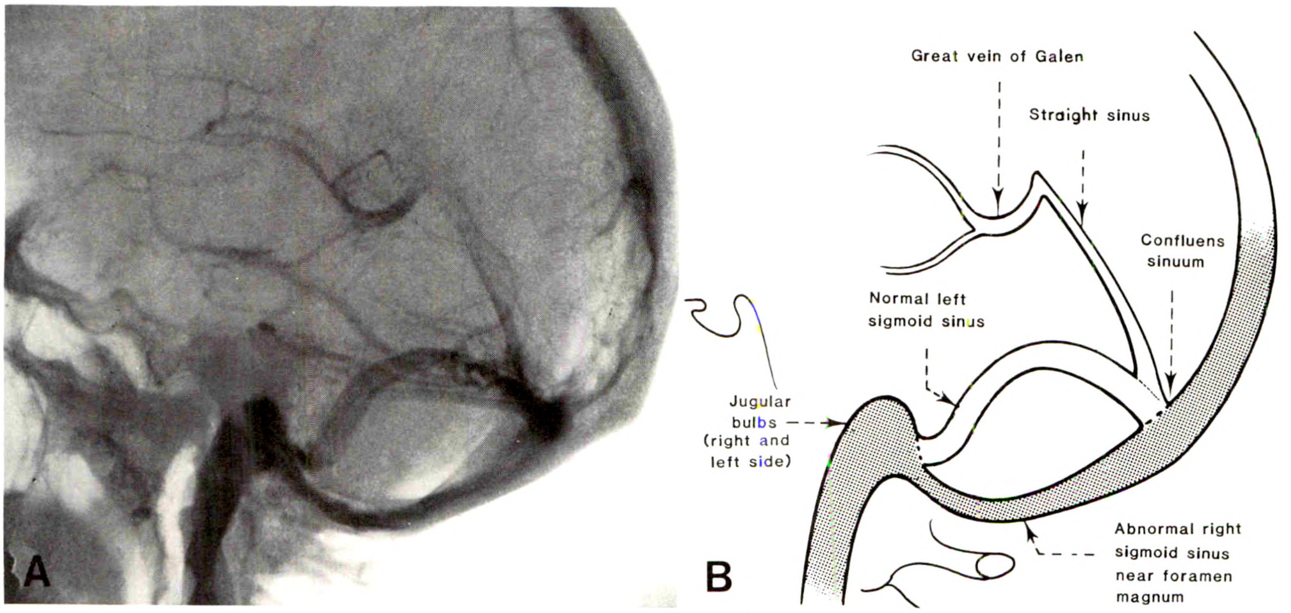
A
B
Great vein of Galen
Straight sinus
Confluens sinuum
Normal left sigmoid sinus
Jugular bulbs (right and left side)
Abnormal right sigmoid sinus near foramen magnum

Fig. 1. A) Lateral projection. Subtraction film from the angiogram in late venous phase. B) Drawing of the same picture. The abnormal right sigmoid sinus has an abnormal downwards direction compared to the normal left transverse and sigmoid sinus.

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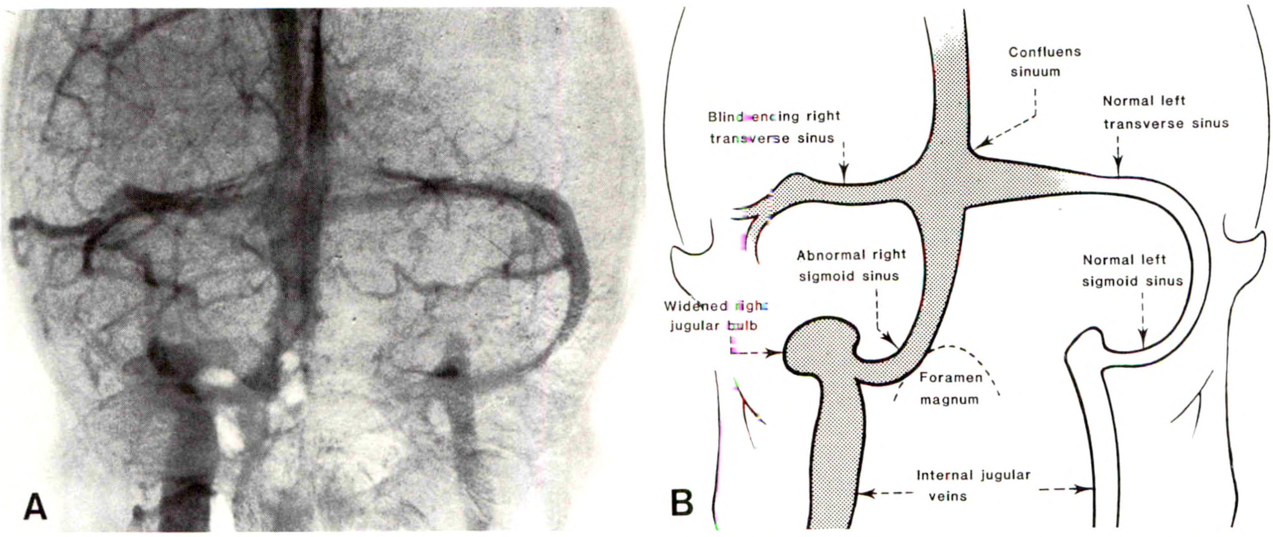
A
B
Confluens sinuum
Blind-ending right transverse sinus
Normal left transverse sinus
Abnormal right sigmoid sinus
Normal left sigmoid sinus
Widened right jugular bulb
Foramen magnum
Internal jugular veins

Fig. 2. A) Frontal half axial projection. Subtraction film from the angiogram in the same late venous phase as in Fig. 1. B) Drawing of the same picture. The abnormal right sigmoid sinus is running straight downward from the confluence sinuum, passing near foramen magnum and upward to the jugular bulb making a sharp angle with the internal jugular vein. Note the blind ending right transverse sinus.

of the fact that no progress of the symptoms had been noted, the case was once again analyzed and discussed. New tomograms revealed a wide jugular fossa on the right side. The jugular fossa had, however, not changed in shape or size during the preceding ten years. No bony wall could be seen between the wide jugular fossa and the hypotympanum. These findings corresponded well with a lack of Brown's sign with the pneumatic otoscope.[2]

The 10-year-old angiograms were reexamined after subtraction of the films.[3] A right-sided sigmoid sinus in its normal place could not be identified. The right transverse sinus continued straight downward from the confluence of sinuses instead of horizontally to the right. The sinus passed close to the foramen magnum, turned upward toward the right jugular fossa where the sigmoid sinus now returned downward in the jugular vein after a sharp angle in the widened jugular fossa (Figs. 1 and 2). The jugular bulb fitted very well in the jugular fossa as seen on the tomograms. There were no signs of space-occupying tumor in the jugular bulb at the angiograms. It was concluded that the transverse and sigmoid sinuses had an abnormal route without aplasia. The patient was discharged without any further treatment.

DISCUSSION

During fetal life the two cardinal veins develop into the intracranial sigmoid sinus and the extracranial internal jugular vein. The connecting link between the sigmoid sinus and the internal jugular vein is the jugular bulb situated in the jugular fossa. The jugular bulb lies under the floor of the middle ear, generally covered with bone. However, according to Overton and Ritter,[4] the jugular bulb extends above the inferior part of the sulcus tympanicus in 6% examined. Körner[5] found dehiscences in the bony wall between the middle ear and the jugular bulb in about 7%. In our patient there may be a combination of abnormal fetal development of the sinuses and lack of bony border between the middle ear and the jugular fossa. Tomograms of the jugular area with a 10-year interval showed no difference in shape and size of the jugular bulb. This indicates no progressive erosion of the jugular fossa caused by the unusually sharply angled bloodstream in the fossa. There is no reason to believe that there has been an increase in the size of the jugular fossa with a further protrusion of the jugular bulb into the middle ear. It is well known that the size of the sigmoid sinus varies, often with the right sinus larger than the left.[5] It is also well known that the venous outflow (drainage) in the transverse and sigmoid sinuses normally may be asymmetric without aplasia of the sinuses.[6]

Turbulence in the blood flow may produce sound waves which could be registered and explain a pulsatile tinnitus.[7] In our patient there had always been a minor tinnitus which, however, had not become worse and had always been of the same magnitude. These findings are interesting to compare with those of Graham,[8] who presented a case where a progressive erosion of the jugular fossa was accompanied by an increased pulsatile tinnitus during the same period.

The unilaterally abnormal venous drainage in our patient, near the foramen magnum to the jugular bulb instead of through the normal sigmoid sinus, has to our knowledge not been described previously. When studying the sinuses the angiographic series must be long enough to include the venous phase. It should be kept in mind that the sinuses close to the petrous bone sometimes may be difficult to study without subtraction films.

In conclusion it is necessary to study the venous phase of angiograms carefully with subtraction films in patients with suspicious glomus jugulare tumors when otoneurosurgical procedures are planned.

REFERENCES

1. Deeb ZL, Rotenberg D, Black FO. Aplasia of sigmoid sinus with high-laying jugular bulb. AJNR 1981; 2:187-8.

2. Brown LA. Glomus jugulare tumors of the middle ear: clinical aspects. Laryngoscope 1953; 63:281-92.

3. Ziedses des Plantes BG. Subtraction. Stuttgart: Georg Thieme, 1961.

4. Overton SB, Ritter FN. A high placed jugular bulb in the middle ear: a clinical and temporal bone study. Paper presented at the meeting of the American Medical Association, San Francisco, 1972.

5. Körner O, Grünberg K. Die otitischen Erkrankungen des Hirns, der Hirnheute und der Blutleiter. München und Wiesbaden: J. F. Bergmann, 1925.

6. Taveras JM, Wood EH. Diagnostic neuroradiology. Vol. 2. Baltimore: Williams & Wilkins, 1977.

7. Bradshow P. An introduction to turbulence and its measurement. Oxford: Pergamon Press, 1971:33-4.

8. Graham MD. The jugular bulb: its anatomical and clinical considerations in contemporary otology. Laryngoscope 1977; 87:105-25.

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SEVENTEENTH INTERNATIONAL CONGRESS OF AUDIOLOGY

The Seventeenth International Congress of Audiology will be held on August 26-30, 1984, on the University of California campus in Santa Barbara. The conference is of interest to audiologists, physicians, acousticians, engineers, and others involved with the hearing sciences. For information, direct correspondence to The Seventeenth ICA Secretariat, Speech and Hearing Center, University of California, Santa Barbara, CA 93106.

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KLIPPEL-FEIL SYNDROME WITH CONDUCTIVE DEAFNESS AND HISTOLOGICAL FINDINGS OF REMOVED STAPES

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The Klippel-Feil syndrome is usually associated with sensorineural hearing impairment, but rarely is it associated with conductive or mixed deafness. A 22-year-old female presented with fusion of the cervical vertebrae, torticollis, scoliosis, pterygium colli, the Sprengel deformity with an omovertebral bone, concavity of the thorax and conductive hearing impairment of the right ear. Tympanotomy disclosed an atrophic long process of incus and a fixation of the stapes footplate, and stapedectomy was performed with immediate postoperative improvement of hearing. However, she developed a sudden hearing loss with dizziness soon after she had physical exercise on the 15th postoperative day, and revision surgery revealed a perilymph fistula of the oval window. Histological investigations of the removed stapes showed no specific osseous changes but hyperostosis of the posterior edge of the footplate. The literature is reviewed and the etiology of the conductive deafness and the perilymph fistula is discussed.

The Klippel-Feil syndrome was first mentioned by Haller in 1745, and was characterized by a congenital deformity of the cervical spine in the form of a numerical reduction of the cervical vertebrae due to fusion of the vertebral bodies, and was associated with multiple abnormalities of the musculoskeletal, neural and sensory organs. Its clinical and anatomical features are later well described by Klippel and Feil[1] in 1912.

Deafness is also the common associated anomaly to this syndrome, and the ear anomalies may include unilateral or bilateral deformity of the inner ear, as shown by Schuknecht.[2] However, hearing loss in most of the previously reported cases was of the sensorineural type, and cases showing the conductive or mixed type of hearing impairment associated with this syndrome were rare.

Most of the cases of the Klippel-Feil syndrome were sporadic, and showed little familial occurrence.[3] Although the X-linked trait that is lethal in males was suggested by Gorlin[4] in 1969, autosomal recessive inheritance has also been suggested.[3] Fraser presented a case of the Klippel-Feil syndrome with profound deafness, and stated that there was no obvious simple hereditary pattern after he had reviewed the previously reported cases of this syndrome.[5] As to the sex preponderance, some authors have stated that the syndrome is more common in males[6]; others feel that the incidence is equal in males and females.[7-9] Still other authors feel that the syndrome is seen more commonly in females.[5,10] The association of the Klippel-Feil syndrome with deafness, however, such as Wildervanck syndrome, is found predominantly in females.[11,12]

A variant of the Klippel-Feil syndrome is known as cervico-oculo-acousticus syndrome, described by Wildervanck[13] in 1952. The Wildervanck syndrome is characterized by fusion of two or several cervical vertebrae (Klippel-Feil syndrome), abducens paralysis, retraction of the eyeballs and congenital sensorineural or conductive hearing impairment. The hearing loss may be unilateral or bilateral. The sensorineural deafness may be the result of a Mondini type of cochlear malformation.[2]

Jarvis and Sellars[10] reported a case with conductive deafness in which they found a thick and fixed stapes footplate which they histologically examined. This was the first report on the histology of the stapes from a Klippel-Feil syndrome with conductive deafness.

The purpose of this report is to present another case of the Klippel-Feil syndrome associated with a conductive hearing loss, and to describe the histological findings of the removed stapes.

CASE REPORT

A 22-year-old female visited our hospital, the chief complaint being hearing impairment in the right ear. She first noticed this hearing loss when she was about 10 years of age, but did not remember whether she had had this symptom in her early childhood. Her hearing loss was not progressive but she developed tinnitus in the right ear a few years prior to her visit to the hospital. In the family history, there were no other hereditary diseases or consanguineous marriages, nor congenital anomalies in the four siblings. Her menarche was at 13 years, but her menstrual cycle had been somewhat irregular.

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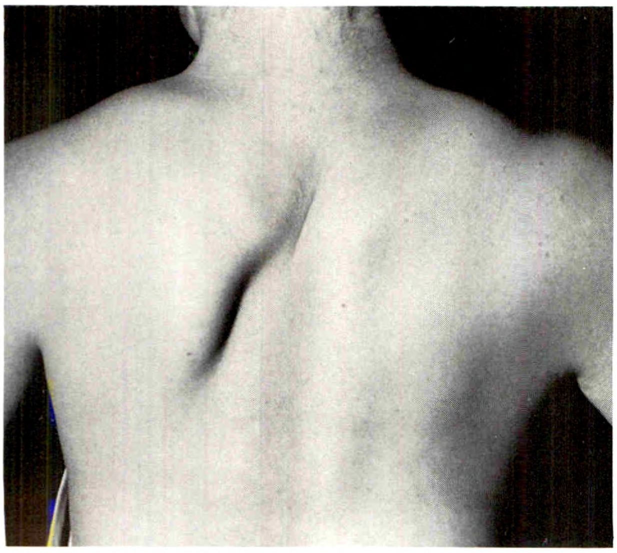

Fig. 1. Posterior view of the patient. Small deformed scapula in high position on left side.

On physical examination, otoscopic findings were normal in both ears. Her head was maintained in a position of torticollis to the left, and there was a slight tendency of pterygium colli more prominently in the left than the right, giving her the appearance of a slight shortening of the neck with a low posterior hairline. The inclination of the head toward the right was somewhat limited, but there was no pain on movement of her head. The left shoulder was adducted forward and elevated, and the left supraclavicular fossa and the superior anterior thorax showed a remarkable concavity. In the back there was a small, prominent, deformed scapula on the left situated at a higher position than the right scapula. The patient was unable to raise her left arm to more than 130° from the trunk (Fig. 1). The pupils reacted equally to light and accommodation. No limitation of lateral gaze was present bilaterally, and no apparent eyeball retraction was found. X-ray studies of the cervical spine showed fusion of the C-5 and C-6 vertebral bodies and posterior arches, suspicious fusion of the C-2 and C-3 posterior arches, and a large omovertebral bone (Fig. 2). A chest x-ray film showed a small left scapula in a high position compatible with the Sprengle deformity. There was a moderate degree of scoliosis to the left in the cervical region. Polytomograms of the temporal bone showed a normal cochlea, vestibule and semicircular canals in each ear.

A pure tone audiogram revealed a conductive hearing loss of an average of 33 dB combined with a bone conduction loss averaging 15 dB at speech frequencies in the right ear (Fig. 3). The speech discrimination was 100% and a tympanogram showed type A. Chromosomal studies using the blood culture technique revealed a normal karyogram.

The diagnosis was made of the Klippel-Feil syndrome with conductive hearing impairment of the right ear, and the patient underwent exploratory tympanotomy under local anesthesia. There was no apparent anomaly in the middle ear except for the atrophic long process of the incus. The stapes footplate, opalescent at the center, but thickened at its posterior half area, was fixed at the stapedeovestibular joint. The oval window margin, particularly at the posterior part, was essentially normal in appearance. The motility of the malleus and incus was intact. The stapes was removed in toto, and a Schuknecht Gelfoam-wire prosthesis was used. Immediate postoperative hearing was remarkably improved, and the patient was discharged from the hospital on the seventh postoperative day. The removed stapes was submitted to histological studies (Fig. 4 A,B). The anterior crus of the stapes was remarkably thickened, while the posterior crus seemed rather thin, but the osseous structure was histologically identical in both crura. There was a remarkable thickening of the entire footplate, but the posterior edge of the footplate showed hyperplastic osseous tissue. With the normal haversian system, the lamellar osseous tissue with few osteocytes was observed. The lamellar structure, however, was rather irregular at the posterior part of the footplate. There was a well-preserved cartilaginous layer in the vestibular surface of the footplate. The connective tissue of the annular ligament was not replaced by any bone or calcification; thus, no definite evidence of bony fixation of the stapes footplate to the oval window niche was detected from these histological specimens.

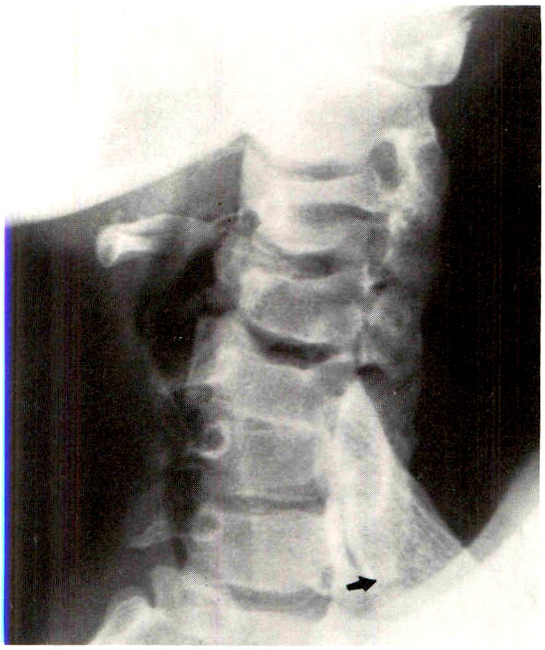

Fig. 2. Cervical spines fused between the C-5 and C-6 vertebral bodies, and suspicious fusion of the C-2 and C-3 posterior arches. Large omovertebral bone (arrow) is noted.

The patient's hearing continued to be stable, until she experienced a sudden hearing change on the

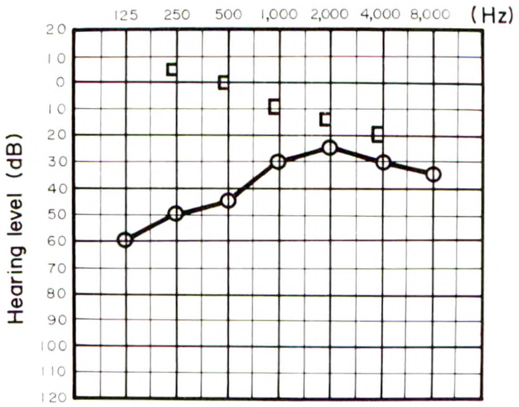

Fig. 3. Pure tone audiogram of right ear showing conductive hearing loss of an average of 33 dB at speech frequencies.

15th postoperative day. Soon after taking what she described as "physical exercise," turning her head to the right and left several times, moving her arms up and down, she developed an obstructive sensation in the operated ear followed by a complete loss of hearing and dizziness. She returned to our clinic, presenting a profound sensorineural deafness on the right ear and spontaneous horizontal nystagmus to the left. The diagnosis of perilymph fistula was made, and revision of the stapedectomy was indicated. During the operation, a perilymph fistula at the inferior, posterior portion of the oval window was detected, and a closure of the fistula with temporalis fascia was performed. However, postoperative audiometry has shown complete absence of any cochlear function in the operated ear.

DISCUSSION

The etiology of the Klippel-Feil syndrome is unknown, but some authors have suggested that the condition arises from a faulty segmentation of the mesodermal somites between the third and seventh week in utero.[14] The first description of the association of deafness with this syndrome was made by Jalladeau[15] in 1936 who reported that deafness was the second most common anomaly, and that nearly 30% were deaf-mute. McLay and Maran[16] reported three cases of this syndrome with profound unilateral or bilateral sensorineural deafness in one of whom the temporal bone was sectioned, and they found that there was underdevelopment of the bony and membranous labyrinth, cochlea and auditory nerve, and that the ossicles from the second arch source were also deformed. The association of conductive or mixed deafness with the Klippel-Feil syndrome has been reported by a few authors.

Singh et al[17] described a patient with a normal middle ear cavity and normal ossicular chain, concluding that the conductive deafness might be due to a defect at the transmission level of the inner ear. Edwards[18] described a female with mixed deafness with this syndrome showing a deformed ossicular chain, and he performed reconstruction of the sound-transmitting chain by the polyethylene strut technique with good results. In 1978, Daniilidis et al[19] reported stapes fixation in a patient with this syndrome, and when removing the fixed stapes, they encountered perilymph gusher. In 1980, they also reported a case of this syndrome associated with conductive deafness, in which the fixation of the stapes was treated well by stapedectomy.[20] The Klippel-Feil syndrome, in its association with conductive or mixed hearing loss, may also be associated with a variety of other developmental anomalies. Jaffee[21] reported a female with multiple anomalies, including the Klippel-Feil syndrome, Sprengel deformity, Turner syndrome, agnesia of the kidney and bilateral mixed deafness. Park et al[22] in 1971 reported the Klippel-Feil syndrome associated with conductive deafness and absent vagina in two unrelated patients. Our case presented fusion of the cervical vertebrae, torticollis, scoliosis, webbed neck, shortness of the neck with a low nuchal hairline, the Sprengel deformity which occurs so frequently that many authors consider it an essential part of the syndrome,[14] and conductive deafness.

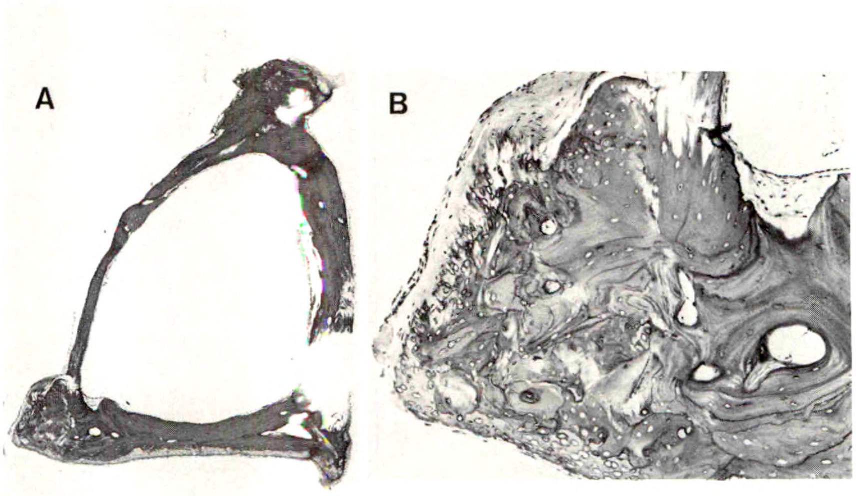

Fig. 4. A) Microphotograph of removed stapes. Note thin posterior crus and thick anterior crus. Entirely thickened footplate, particularly at posterior edge of footplate. Cartilaginous tissue of vestibular surface is well preserved. B) High power view of posterior part of footplate. Hyperostotic change with few osteocytes and irregular structure of lamellar bone are shown. Annular ligament is not calcified nor invaded by new bone formation.

Besides these symptoms, our case presented remarkable concavity of the supraclavicular fossa and the upper anterior thorax, as well as the large omovertebral bone. From these clinical manifestations, our case could be differentiated from the Wildervanck syndrome, the Klippel-Feil syndrome associated with hearing loss and absent vagina, and the syndrome described by Jaffee.

It is well known that leakage of cerebrospinal fluid may happen spontaneously with a congenital perilymph fistula when there is a known congenital defect of the middle ear or inner ear in association with syndromes such as the Klippel-Feil syndrome.[23,24] It has also been clearly demonstrated that fistulization of the oval window can occur after stapedectomy or in a normal ear after head injury or physical exertion.[25,26] Possibly, the ear in question might have suffered from another malformation in the labyrinth which would make it susceptible to development of a perilymph fistula when submitted to a sudden increase of intracranial cerebrospinal fluid pressure, presumably induced by physical exercise, although during stapedectomy there was no abnormal extravasation of perilymph. As mentioned earlier in this report, Jarvis and Sellars[10] published the first description of a histological investigation of the stapes from a case of the Klippel-Feil syndrome with conductive deafness. They found that there were irregular cement lines of bone which did not suggest otosclerosis. They concluded that the stapes fixation was due to underlying mesenchymal dysplasia.

The histological changes of the removed stapes in the present case were nonspecific hyperostotic changes of the entire footplate, particularly at the posterior edge of the footplate, and the annular ligament and circumferential part of the footplate itself were apparently well preserved. There was no evidence of otosclerotic focus in any part of the footplate. Since the etiology of fusion of the cervical vertebrae is believed to be faulty segmentation of the mesodermal somite, a common etiologic factor of fusion of the cervical vertebrae and stapes fixation can be considered. The stapes footplate is histologically continuous to the cartilaginous otic capsule, and it is believed that the thinning out and specific differentiation of a marginal zone forms the annular ligament, with the footplate becoming a separate mobile structure.[27-29]

If faulty segmentation of the precartilaginous lamina stapedius from the otic capsule and fusion of the cervical vertebrae are induced by the same intrauterine etiologic influence, osseous fixation of the footplate may also be possible, resulting in congenital fixation of the stapes. However, the oval window margin in our case was apparently normal, thus ruling out an abnormality of configuration caused by, for instance, a developmental anomaly or localized bone dysplasia.

Therefore, we concluded that there was no common cause of misdifferentiation of the cervical vertebrae and the stapes footplate. In the present case, however, the removed stapes which was observed in the histological sections did not provide definite or explainable evidence for the immobilization of the stapes footplate, producing the conductive deafness in this patient. Since the annular ligament and the articular surface of the stapedial footplate were intact, we can assume that in the absence of an otosclerotic focus, a localized area of hyperostosis was responsible for the impingement of the footplate, resulting in the conductive deafness of the patient.

ACKNOWLEDGMENT — The authors would like to thank Mrs. Marian Holm-Hansen for her assistance in the preparation of this manuscript.

REFERENCES

1. Klippel M, Feil A. Un cas d'absence des vertebres cervicales avec cage thoracique remontant jusqu'á la base du crâne. Nouvelle Inconographic de las Salpêtrière 1912; 25:223-50.

2. Schuknecht HF. Mondini dysplasia, a clinical and pathological study. Ann Otol Rhinol Laryngol 1980; 80 Suppl 65.

3. Gunderson CH, Greenspan RH, Glaser GH, Lubs HA. The Klippel-Feil syndrome: genetic and clinical reevaluation of cervical fusion. Medicine 1967; 46:491-512.

4. Gorlin RJ, Sedano H. Klippel-Feil syndrome. Mod Med 1969; 37:146-7.

5. Fraser GR. Profound childhood deafness. J Med Genet 1964; 1:118-51.

6. Nobel TP, Frawley JM. Klippel-Feil syndrome. Numerical reduction of cervical vertebrae. Ann Surg 1925; 82:728-34.

7. Bauman GI. Absence of the cervical spine: Klippel-Feil syndrome. JAMA 1932; 98:129-32.

8. DeWillard FP, Nicholson JT. Klippel-Feil syndrome. Ann Surg 1934; 99:561-7.

9. Greig DM. Congenital high-scapula and a consideration of brevicollis. Edinburgh Med J 1924; 31:22-44.

10. Jarvis JF, Sellars SL. Klippel-Feil deformity associated with congenital conductive deafness. J Laryngol Otol 1974; 88:285-9.

11. Everberg G, Ratjen E, Sorensen H. Wildervanck's syndrome. Klippel-Feil's syndrome associated with deafness and retraction of the eyeball. Br J Radiol 1963; 36:562-7.

12. Gorlin RJ. Klippel-Feil anomalad. In: Gorlin RJ, Pindborg JJ, Cohen MM, eds. Syndromes of the head and neck. New York: McGraw-Hill 1976; 408-11.

13. Wildervanck LS. Een geval van aandoening van Klippel-Feil gecombineerd mel abducens paralyse, retractio bulbi en doofstomheid. Ned T Geneesk 1952; 96:2752.

14. Shoul MI, Ritvo M. Clinical and roentgenological manifestations of the Klippel-Feil syndrome. Am J Roentgenol 1952; 68:369-85.

15. Jalladeau J. Malformations congenitales associees au syndrome de Klippel-Feil. Thesis, Paris: 1936.

16. McLay K, Maran AGD. Deafness and the Klippel-Feil syndrome. J Laryngol Otol 1969; 83:175-84.

17. Singh SP, Rock EH, Shulman A. Klippel-Feil syndrome

with unexplained apparent conductive hearing loss. A case report. Laryngoscope 1969; 79:113-7.

18. Edwards WG. Congenital middle-ear deafness with anomalies of the face. J Laryngol Otol 1964; 74:152-70.

19. Daniilidis J, Maganaris T, Dimitriadis A, Iliades T, Manolidis L. Stapes gusher and Klippel-Feil syndrome. Laryngoscope 1978; 88:1178-83.

20. Daniilidis J, Demetriadis A, Triaridis C, Manolidis L. Otological findings in cervico-oculo-auditory dysplasia. J Laryngol Otol 1980; 94:533-44.

21. Jaffee IS. Congenital shoulder-neck-auditory dysplasia. Laryngoscope 1968; 78:2119-39.

22. Park IJ, Jones HW, Nager GT, Chen SCA, Hussels IE. A new syndrome in two unrelated females: Klippel-Feil deformity, conductive deafness and absent vagina. Birth Defect, original article series 1971; 7:311-3.

23. Glasscock ME. The stapes gusher. Arch Otolaryngol 1973; 98:547-52.

24. Gacek R, Leipzig B. Congenital cerebrospinal otorrhea. Ann Otol Rhinol Laryngol 1979; 88:358-65.

25. Fee GA. Traumatic perilymphatic fistulas. Arch Otolaryngol 1968; 88:477-80.

26. Olson NR, Lehman RH. Cerebrospinal fluid otorrhea and the congenitally fixed stapes. Laryngoscope 1968; 78:352-60.

27. Strickland EM, Hanson JR, Anson BJ. Branchial sources of auditory ossicles in man. I. Literature. Arch Otolaryngol 1962; 76:100-22.

28. Hanson JR, Anson BJ, Strickland EM. Branchial sources of the auditory ossicles in man. Part II. Observations of embryonic stages from 7 mm to 28 mm. Arch Otolaryngol 1962; 76:200-15.

29. Schuknecht HF. Pathology of the ear. Massachusetts: Harvard University Press, 1974:165-213.

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AMERICAN BOARD OF OTOLARYNGOLOGY EXAMINATION

The American Board of Otolaryngology's written examination will be given September 25, 1983, at the Palmer House in Chicago, Illinois. Registration will be held Saturday, September 24, 1983, at 5:00 PM at the Palmer House. It is estimated that the examination will conclude at 6:00 PM Sunday.

Deadline for application is May 1. Please contact George F. Reed, MD, Secretary-Treasurer, at the American Board of Otolaryngology, 220 Collingwood, Suite 130, Ann Arbor, MI 48103, for new application forms.

Ann Otol Rhinol Laryngol 92:1983

X-RAY STUDY OF THE MONTH

PETROUS CAROTID ANEURYSM

John R. Hesselink, MD
Alfred L. Weber, MD
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PATIENT

A 48-year-old man presented with gradual hearing loss in the left ear over a 20-year period. Two months prior to admission, he had an episode of sharp pain in the left ear with headache. An acute otitis media with a perforated ear drum was found and he was treated appropriately with antibiotics. At the time of admission, examination revealed a hemotympanum with a bluish pulsatile mass in the tympanic cavity. Audiogram demonstrated a moderate conductive hearing loss on the left which was more significant at higher frequencies.

RADIOGRAPHIC FINDINGS

The lateral polytome section (Fig. 1A) of the petrous bone shows erosion of the jugular spine. A thin curvilinear density (arrowhead) represents a remnant of bone or more likely calcification within the wall of the aneurysm. On the AP polytome section (Fig. 1B,C) at the cochlear and vestibular level there is erosion of the floor of the tympanic cavity and carotid canal. The carotid canal and jugular fossa form a single cavity (arrowheads). Carotid arteriograms in AP (Fig. 1D) and oblique (Fig. 1E) projections demonstrate an aneurysm of the petrous segment of the internal carotid artery. The aneurysm extends laterally and superiorly into the middle ear region (arrowheads).

DISCUSSION

The petrous segment of the internal carotid artery is a relatively uncommon location for aneurysms, with approximately a dozen cases being reported in the literature. They may be congenital,[1,2] but are more commonly associated with trauma[3] or chronic otitis media.[4] In temporal bone fractures involving the carotid canal, associated injury to the vessel wall probably predisposes the artery to aneurysm formation. Inadequate treatment of middle ear infections may result in erosion of the thin bony plate separating the vertical portion of the carotid canal and the tympanic cavity, exposing the carotid artery.

The clinical presentation depends on the direction of expansion of the aneurysm.[5] Medial extension to the petrous apex and cavernous sinus region may lead to cranial nerve palsies. Extension into the

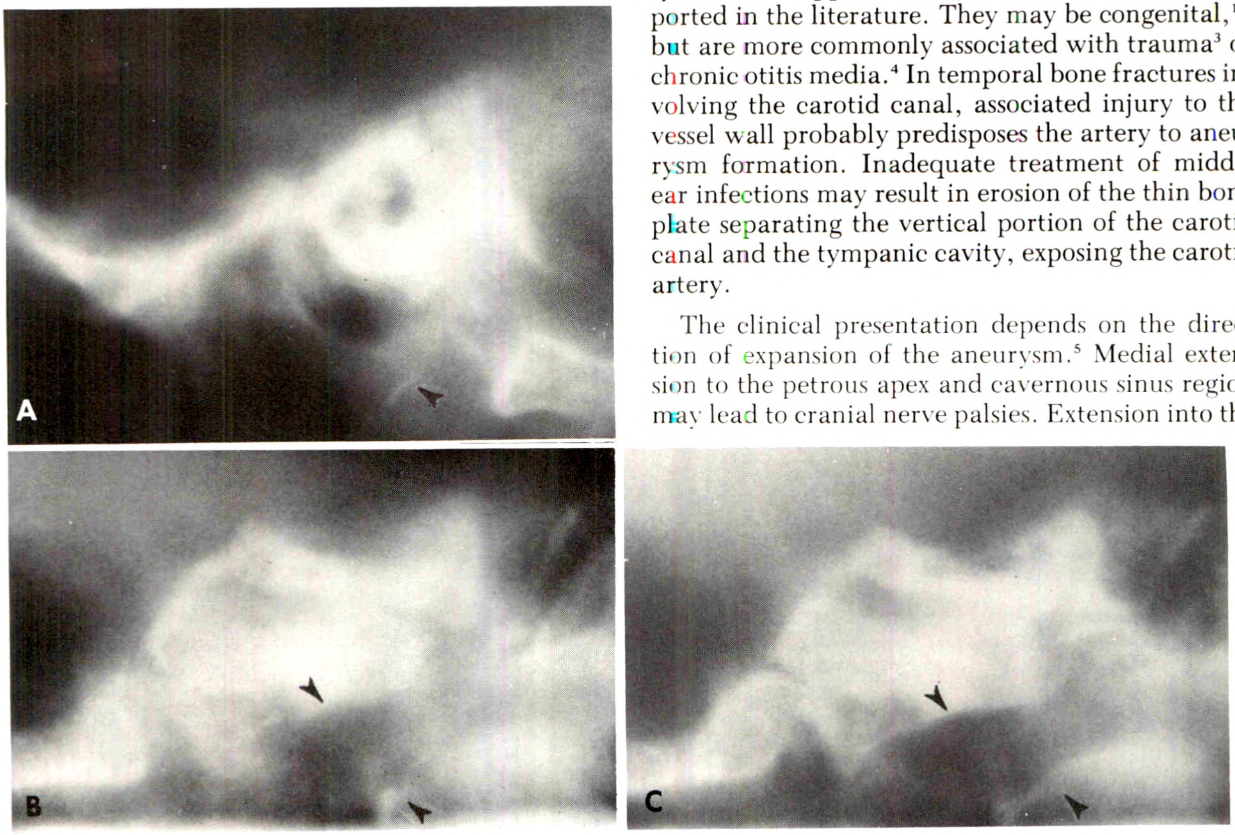

Fig. 1A-C

From the Department of Radiology, Massachusetts Eye and Ear Infirmary, Boston.

REPRINTS — Alfred L. Weber, MD, Department of Radiology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

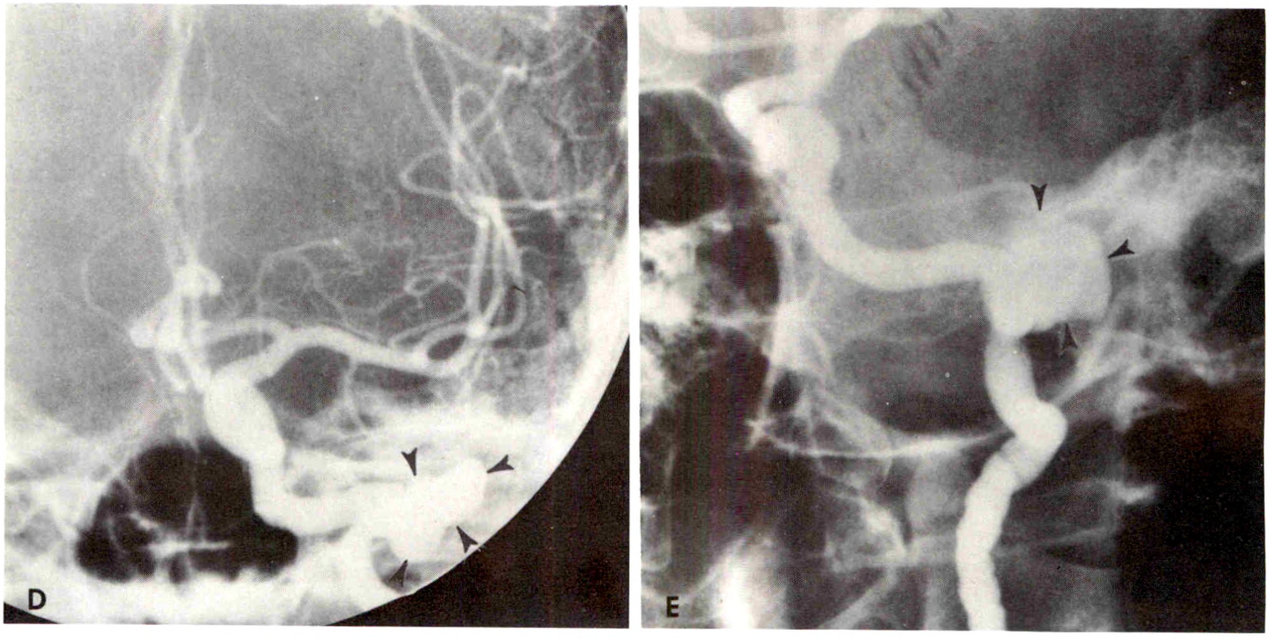

Fig. 1D, E

tympanic cavity is associated with hearing loss, tinnitus and pulsatile mass on examination. These patients may present with aural hemorrhage or epistaxis. To suspect the diagnosis in cases with epistaxis requires an astute clinician to observe the blood or clot at the eustachian tube orifice.[3]

The differential diagnosis includes aberrant carotid artery presenting in the middle ear, aberrant course of the jugular vein and glomus tympanojugulare tumor. The preferred treatment is ligation of the internal carotid artery in the neck. The intracranial hemodynamics must be evaluated thoroughly at the time of preoperative angiogram. If the potential collaterals to that cerebral hemisphere are inadequate, the carotid ligation should be preceded by a superficial temporary artery to middle cerebral artery bypass graft.

In the case presented here, the aneurysm was probably of congenital origin. The history of otitis media did not seem sufficient to make infection a possible causative factor. The episode of acute ear pain and the hemotympanum at the time of admission were probably related to small hemorrhages of the aneurysm. Fortunately these initial bleeds were not fatal.

REFERENCES

1. Allen GW. Angiography in otolaryngology. Laryngoscope 1967; 77:1909-61.

2. Guirguis S, Tadros FW. An internal carotid aneurysm in the petrous temporal bone. J Neurol Neurosurg Psychiatry 1961; 24:84-5.

3. Busby DR, Slemmons DH, Miller TF. Fatal epistaxis via carotid aneurysm and eustachian tube. Arch Otolaryngol 1968; 87:295-8.

4. Barrett JH, Lawrence VL. Aneurysm of the internal carotid artery as a complication of mastoidectomy. Arch Otolaryngol 1968; 87:295-8.

5. Harrison TH, Odom GL, Kunkle EC. Internal carotid aneurysm arising in carotid canal; report of a case with extension to the gosserian ganglion. Arch Neurol 1963; 8:328-31.

Ann Otol Rhinol Laryngol 92:1983

PATHOLOGY CONSULTATION

PAROTID GLAND AND ITS LYMPH NODES AS METASTATIC SITES

JOHN G. BATSAKIS, MD
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The parotid gland and its lymph nodes can serve as metastatic sites from regional and distant primary neoplasms. In the head and neck, the regions and neoplasms at risk for such metastases are melanomas and squamous cell carcinomas of the skin of the eyelids, frontal, temporal, posterior cheek and anterior ear regions. The mucous membranes of the upper aerodigestive tract may also be a site for a primary demonstrating parotid area metastases.

Metastatic involvement (in the broadest context) of the parotid gland may arise a) from lymphatic spread, b) from hematogenous dissemination, or c) by contiguous extension. The latter is common with supporting tissue malignancies of the parotid region while the parotid gland as a focus of metastasis from a distant primary is unusual.

Lymphatic metastases to the gland may be direct without involvement of the paraglandular or extraglandular lymph nodes, may be secondary from a metastatic focus in a paraglandular lymph node, or may be from a retrograde extension from massive metastases in the neck.

The parotid gland and the juxtaparotid area is rather abundantly supplied by lymph nodes and lymphatics.[1-3] The lymph nodes may be divided into intraglandular and extraglandular groups. An average of 20 intraparotid lymph nodes may be identified after serial sectioning of the normal parotid gland. These are definable nodes with capsules and sinuses and their number does not include the normally present aggregates of lymphocytes and lymphoid tissue without nodal characteristics. Intraglandular nodes are located along the posterior facial vein between the superficial and deep parts of the parotid gland and are both superficial and deep to the facial nerve. Extraglandular nodes are usually subdivided into preauricular and infra-auricular groups and are predominantly in the preauricular area, along the superficial temporal vessels.

The intraglandular and extraglandular groups, while separable by the topography, are a single functional unit. Afferent lymphatics arise from the lateral and frontal scalp, eyelids, conjunctivae, lacrimal gland, molar area, root of nose, external auditory meatus, eustachian tube, and cranial vault. The sinonasal, nasopharyngeal and oropharyngeal regions also have lymphatic connections. While epithelial malignancies of these sites are all capable of yielding parotid node metastases, the high-risk group of patients are those with deeply invasive melanomas or poorly differentiated squamous cell carcinomas in the skin of the ipsilateral eyelid, frontal, temporal, posterior cheek and anterior ear regions.[4]

The paraglandular lymph nodes are most often the sites of the metastases. These are relatively more abundant in the pretragal and supratragal areas. The anterior portion of the parotid gland is rarely involved as a metastatic focus in either intraglandular or paraglandular lymph nodes.[1]

In accordance with the risk potential, the predominant histologic types of metastases are melanomas and squamous cell carcinomas. On occasion the metastasis may be present as a lesion from an "occult" primary.

Carcinomas and melanomas of mucosal surfaces involve the parotid group of lymph nodes less frequently but they, too, may present as the signal metastasis. Distant sites with metastases to the parotid region and parotid gland are unusual and are led by the carcinomas of the kidney, lung and breast.

Metastases to the two parotid groups of lymph nodes may not only pose problems in clinical assessment of the presenting mass, they also often perplex the pathologist, particularly one who is unaware of the aggregation of lymph nodes in this region. Unless the lymph node is overrun by the metastasis, the identification of its capsule and circumscription from the parotid parenchyma serves to point to a lymphatic metastasis. The dominance of melanoma and squamous cell carcinoma in the statistics of tumors metastatic to the parotid further serves as a distinction since both of these malignancies are rare as parotid gland primaries. Hematogenous metastases, besides their histologic differences from pri-

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REPRINTS — John G. Batsakis, MD, Chairman, Department of Pathology, M. D. Anderson Hospital, Texas Medical Center, Houston, TX 77030.

mary neoplasms of the parotid gland, usually involve the interlobular and intralobular fibrous septae of the gland, only secondarily extending into the parenchyma.

Metastatic malignancy in the parotid gland lymph nodes is usually an ominous prognostic sign that is worsened by concomitant cervical lymph node metastases.[1,2] Some enhancement may be provided by surgical excision coupled with postoperative irradiation. In the series reported by Cassisi et al[2] the recurrence rate in the parotid gland/ipsilateral neck was reduced from 75% to 20% by this combination therapy.

SUMMARY

An awareness of the possibility and probability of metastatic lesions to the parotid gland and its lymph nodes may save embarrassment to the pathologist and significantly alter surgical management of the patient. Most often the primary is known and predicted from regions of high risk. At other times the metastasis may clinically appear without a demonstrable or known primary. In either instance prognosis is diminished by the metastases.

REFERENCES

1. Conley J, Arena S. Parotid gland as a focus of metastasis. Arch Surg 1963; 87:757-64.

2. Cassisi NJ, Dickerson DR, Million RR. Squamous cell carcinoma of the skin metastatic to parotid nodes. Arch Otolaryngol 1978; 104:336-9.

3. Pope TH Jr, Lehmann WB. Regional metastasis to parotid nodes. Arch Otolaryngol 1967; 86:673-5.

4. Storm FK, Eilber FR, Sparks FC, Morton DL. A prospective study of parotid metastases from head and neck cancer. Am J Surg 1977; 134:115-8.

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SATELLITE SYMPOSIUM ON PEDIATRIC OTOLARYNGOLOGY

A Satellite Symposium on Pediatric Otolaryngology will be held October 17, 1983, in Tokyo. For further information, contact Keijiro Koga, Department of Otolaryngology, National Children's Hospital, 3-35-31, Taishido Satagayaku, Tokyo, Japan.

LETTERS TO THE EDITOR

Dear Editor,

The paper by Mirko Tos and Jens Thomsen, "The Price of Preservation of Hearing in Acoustic Neuroma Surgery," *(Ann Otol Rhinol Laryngol* 1982; 91:240-5) presents some arguments for the translabyrinthine approach. But their demonstration would be much more forceful if the authors had also mentioned the many references supporting the view that it is possible and worthwhile to preserve hearing in acoustic neuroma surgery (listed below). The title of their paper is somewhat misleading; the paper is more concerned with the translabyrinthine approach than with the preservation of hearing.

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REFERENCES

1. Chai WX. Preservation of facial and acoustic nerves in the total removal of large and small acoustic tumors. Report of two cases. J. Neurosurg 1981; 54:268-72.

2. Fischer G, Constantini JL, Mercier P. Improvement of hearing after microsurgical removal of acoustic neurinoma. Neurosurgery (Baltimore), 1980; 7:154-9.

3. Malis LI. Microsurgical treatment of acoustic neurinomas. In: Handa H, ed. Microneurosurgery. Baltimore: University Park Press, 1975:105-20.

4. Ojemann RG, Crowell RC. Acoustic neuromas treated by microsurgical suboccipital operations. Prog Neurol Surg 1978; 9:337-73.

5. Sugita K, Kobayashi S, Mutsuga N, et al. Microsurgery for acoustic neurinoma: lateral position and preservation of facial and cochlear nerves. Neurol Med Chir (Tokyo) 1979; 19:637-41.

Dear Editor,

Recently, Yarington and Thompson (Incendiary characteristics of endotracheal tubes with the carbon dioxide laser: supplemental report. *Ann Otol Rhinol Laryngol* 1982; 91:605) reported a follow-up to their paper on the incendiary characteristics of endotracheal tubes in regard to ignition during endoscopic laser surgery. They stated that the silicone rubber tube is resistant to combustion in an environment of 20% oxygen. We have similarly been studying the incendiary characteristics of various endotracheal tubes including the silicone tube. While our data support their findings that the silicone tube is relatively safe when tested or used under the specific conditions stated in their paper, these test conditions do not mimic common clinical use. Under conditions closer to those found in common practice, the safety afforded by the use of the silicone tube may be seriously compromised.

Anesthesia for short procedures such as endoscopic laser surgery is commonly conducted using a mixture of oxygen and nitrous oxide. We and other workers (eg, Hirshman and Smith, Arch Otolaryngol 1980; 106:639-41) have found that *nitrous oxide supports combustion at least as well as oxygen.* Indeed, with a flowing mixture of 20% oxygen in nitrous oxide, ignition of a silicone endotracheal tube is virtually instantaneous (0.1 second exposure at 8 W of laser power) and violent if the beam strikes the interior of the tube through a small hole.

Like Yarington and Thompson, we have failed to achieve ignition of a silicone tube with oxygen concentrations below 30% where nitrogen or helium (there was no noticeable difference) was the diluent. Furthermore, regardless of the gas mixture inside the tube, no ignition occurred when the point of exposure was the exterior of the tube in an atmosphere of air. However, our laser, a rather venerable Coherent 400, experiences a large fall-off in power when used in continuous mode. A more powerful laser may be able to penetrate the tube and reach the dangerous atmosphere inside. Furthermore, ignition *has* been achieved if the atmosphere outside the tube contains excess oxygen or nitrous oxide, as may be the case if there is leakage past the cuff.

A potential hazard has also been noted which may be unique to the silicone tube. Upon combustion, silicone tubes revert to a powdery ash with no physical strength. Several of our tubes have rapidly separated at the point of ignition. Were this to occur in a patient, the burning distal end of the tube would be difficult to remove, exacerbating an already dangerous situation. On the other hand, in a test of a wire-reinforced silicone tube, the distal end was retained by the reinforcing wire despite disintegration of the section of the tube at the point of ignition.

In summary, we would like to agree with Yarington and Thompson that the silicone endotracheal tube provides a fair degree of safety for endoscopic laser surgery of the upper aerodigestive tract, but only if the following considerations are kept in mind: 1) the inspired oxygen concentration should not exceed 30%; 2) nitrous oxide should not be used, the oxygen being delivered in either air, nitrogen or helium; 3) should oxygen concentrations higher than 30% be necessary, exposure time should be brief and laser power kept as low as possible to avoid penetrating the tube, and no leakage past the cuff should be permitted; 4) a wire-reinforced tube is preferable to insure complete withdrawal should ignition occur.

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BOOKS RECEIVED

How to Write and Publish Papers in the Medical Sciences

By Edward J. Huth. Black and white illustrations, indexed, hard and soft covers, 196 pages, 1982. ISI Press, Philadelphia, $17.95 and $11.95.

Forensic Audiology

Edited by Marc B. Kramer and Joan M. Arnbruster. Black and white illustrations, indexed, hard cover, 337 pages, 1982. University Park Press, Baltimore, $44.95.

Jacques Joseph: Surgical Sculptor

By Paul Natvig. Black and white illustrations, indexed, hard cover, 112 pages, 1982. W. B. Saunders, Philadelphia, $27.50.

Principles of Speech Audiometry

Edited by Dan F. Konkle and William F. Rintelmann. *Perspectives in Audiology* series. Black and white illustrations, indexed, hard cover, 395 pages, 1983. University Park Press, Baltimore, $39.95.

BOOK REVIEWS

The Primary Acoustic Nuclei

By *Rafael Lorente de Nó.* Hard cover, black and white illustrations, indexed, 177 pages, 1981. Raven Press, New York, $32.

This book is a revision and completion of a manuscript first drafted in 1938. For over 30 years the manuscript and numerous drawings rested in a cabinet, "virtually forgotten," in the words of the author. However, those few investigators who were studying the cochlear nucleus were aware of Dr. Lorente's plan to finish his manuscript someday but had despaired of ever seeing the promised drawings. Following retirement from The Rockefeller Institute in the mid-1970s, Dr. Lorente joined Dr. Victor Goodhill and his colleagues in the Division of Head and Neck Surgery at UCLA, where he was given the opportunity to prepare the present monograph. There followed several publications, one in a supplement to the *Annals of Otology, Rhinology & Laryngology*[1] and the other in Goodhill's book.[2] The present volume includes the illustrations from these papers and some of the earlier ones, principally those published in 1933[3,4] and 1937.[5] In addition there is a large number of previously unpublished drawings bearing dates from the 1930s and a few which were evidently made in recent years.

The greatest value of this book is without a doubt the many exquisite drawings made from the author's observations with the Golgi methods on newborn or very young kittens. There are 130 illustrations, mostly line drawings of neurons and axonal endings from Golgi impregnations, but also some photomicrographic reproductions of Nissl-stained and myelin-stained sections. This material is arranged in six chapters, as follows: 1) terminal territories of the cochlear nerve; 2) myelinated elements of the primary acoustic territory; 3) structure of the ventral nucleus; 4) structure of the posterior lateral and interfascicular nuclei; 5) cellular architecture of the tuberculum acusticum and neighboring nuclei; 6) structure of the cortex of the tuberculum acusticum. These chapters are filled with many delectable details of neurons, axons and dendrites from practically every corner of the cochlear nuclei. There is so much information that this reviewer, no stranger to Golgi studies of the nucleus, has taken the better part of a year to review it. It may, therefore, come as a surprise to the reader to learn that this account is far from complete. Thus, one reads on page 60 that "the information presented on the anterior branches of division of the cochlear nerve fibers is far more detailed than that available in the literature, either classical or contemporary. Nevertheless, the information is only fragmentary. . . ."

By way of criticism one should note that there is no explanation of how the drawings were made — with camera lucida or freehand — and no magnifications are given for any of the illustrations, nor is the problem of extrapolating results from very young kittens to the mature state discussed. The text accompanying the figures is hard to follow, even for experts who have worked with the very same methods. This partly reflects the unabashedly dogmatic style of the author. For example, we are told that certain cochlear fibers in the organ of Corti could not be efferent because "in the Golgi section used to prepare Fig. 1-1 fibers of the efferent system were not stained." Many other examples could be cited. Dr. Lorente informs us that "no clear correspondence exists between the subdivisions of the ventral and posterior nuclei described in this volume and the subdivisions proposed by Brawer and colleagues.[6]" Thus, in one stroke the author has denied us the opportunity to compare his observations with virtually all of the modern work on the cat cochlear nucleus with the Golgi methods, which is after all based on Brawer et al. However, the cytoarchitectonic material presented by the author does not show any particular discrepancy with Brawer et al. This raises another problem.

It is difficult to relate this work to modern neuroanatomical and neurophysiological studies. Although the author attempts to incorporate some of the literature of the last 40 years since his remarkable studies were done, his understanding of modern methods is limited. Thus, his criticism of Rasmussen's findings on centrifugal pathways to the cochlear nuclei betrays ignorance of the silver degeneration methods, which have been in use for over 25 years. More telling perhaps is absence of any reference to the electron microscope literature or attempts to correlate the neuronal and synaptic morphology of the cochlear nucleus to acoustic response properties. One wonders why the author has failed to quote the studies of Cant and Morest,[7-9] who demonstrated an abundance of centrifugal projections to the rostral pole of the ventral cochlear nucleus — which Dr. Lorente's material did not reveal. Perhaps this omission reflects the fact that "the revision was closed early in 1979." On the other hand, there is no mention of the work of Kane[10] on the dorsal cochlear nucleus, which clearly contradicts the author's notion that the dorsal cochlear nucleus can be regarded as "the cerebellum of the acoustic system," despite some superficial similarities. It is probably not the reviewer's prerogative to criticize the author's physiological theories but only to warn unacquainted readers that these are totally at odds with modern viewpoints. All things considered, however, it may be unfair to judge this work for something it was not meant to be. Suffice it to say that this is not a book for the general reader or the amateur but mainly for the delectation of Golgi experts.

Perhaps the greatest significance of the author's work is the detailed approach that he has developed, as a logical consequence of the doctrines of his teacher, Ramón y Cajal. This was to carry the neuron doctrine to its ultimate refinement, namely, that a truly functional neuroanatomy must take account of the individual types of neurons, especially of the projections of the particular kinds of axons. This was expressed in terms of the "chains" of neurons arranged in "circuits." Now widely appreciated as "local circuits," in 1934 this was a bold statement to fling in the face of the Nissl body cytoarchitectonics that prevailed at that time. This concept was most clearly expressed in Dr. Lorente's papers on the limbic cortex[11,12] and the cerebral cortex in general. These works were truly inspirational. Hardly any student of neuroscience over the age of 40 could have escaped the influence of the famous chapter on the structure of the cerebral cortex in Fulton's physiology textbook.[13] Who could forget Professor Fulton's footnote quoting Dr. Lorente's explanation that he had reviewed every detail in his slides before sending in the manuscript? One might have wished for the same treatment of the present material, but surely this was not possible. For example, in the material on cochlear innervation one reads on page 3 that the author attempted to settle a question of interpretation by "studying the original drawing under a magnifying class." One hopes that Dr. Lorente's previous slides are still intact. But at least his wonderful drawings are safely preserved in a suitably sized, well-printed format. Raven Press is to be congratulated for producing a beautiful *opus magnum artis* by one of the grand masters of neuroanatomy.

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REFERENCES

1. Lorente de Nó R. Some unresolved problems concerning the cochlear nerve. Ann Otol Rhinol Laryngol 1976; 85 Suppl 34: 1-28.

2. Lorente de Nó R. Central representation of the eighth nerve. In: Goodhill V, ed. Ear diseases, deafness and dizziness. Hagerstown, Md: Harper & Row, 1979, 64-86.

3. Lorente de Nó R. Anatomy of the eighth nerve. The central projection of the nerve endings of the internal ear. Laryngoscope 1933; 43:1-38.

4. Lorente de Nó R. Anatomy of the eighth nerve. III. General plan of structure of the primary cochlear nuclei. Laryngoscope 1933; 43:327-50.

5. Lorente de Nó R. The sensory endings in the cochlea. Laryngoscope 1937; 47:373-7.

6. Brawer JR, Morest DK, Kane EC. The neuronal architecture of the cochlear nucleus of the cat. J Comp Neurol 1974; 155: 251-300.

7. Cant NB, Morest DK. Axons from non-cochlear sources in the anteroventral cochlear nucleus of the cat. A study with the rapid Golgi method. Neuroscience 1978; 3:1003-29.

8. Cant NB, Morest DK. Organization of the neurons in the anterior division of the anteroventral cochlear nucleus of the cat. A study with the electron microscope. Neuroscience 1979; 4: 1909-23.

9. Cant NB, Morest DK. The bushy cells in the anteroventral cochlear nucleus of the cat. A study with the electron microscope. Neuroscience 1979; 4:1925-45.

10. Kane EC. Synaptic organization in the dorsal cochlear nucleus of the cat: a light and electron microscopic study. J Comp Neurol 1974; 155:301-30.

11. Lorente de Nó R. Studies on the structure of the cerebral cortex. I. The area entorhinalis. J Psychol Neurol 1933; 45: 381-438.

12. Lorente de Nó R. Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. J Psychol Neurol 1934; 46:113-77.

13. Lorente de Nó R. Cerebral cortex: architecture, intracortical connections, motor projections. In: Fulton JF, ed. Physiology of the nervous system. 2nd ed. London: Oxford University Press, 1943, 274-301.

Neurological Surgery of the Ear and Skull Base

Edited by *Derald E. Brackman*. Black and white illustrations, subject index, hard cover, 394 pages, 1982. Raven Press, New York, $68.

Based on papers presented at the third in a series of symposia sponsored by the Ear Research Foundation of Florida and the House Ear Institute in Los Angeles, this book continues to illustrate the creative interchange between neurology and otolaryngology that has characterized otologic surgical development during the past 25 years. In substance and format the present volume represents a continuity with and a departure from its distinguished predecessors edited by Herbert Silverstein and Horace Norrell under the title *Neurological Surgery of the Ear*, volumes 1 and 2, based on the papers given at the first symposia.

Among this book's continuities with its predecessors are good bibliographical references which, apart from a few inexplicable absences, provide an excellent source for further study by otolaryngologists. A clear and substantive presentation of the advantages and disadvantages of important surgical procedures for the retention and preservation of hearing, such as the translabyrinthine, retrolabyrinthine and middle fossa procedures, are set forth in the current volume. An excellent discussion of acoustic neuroma surgery is presented, one which adds new information to that previously published and also fresh insights into this subject.

Certainly the most intellectually satisfying are those essays which are distinguished by that blend of scientific insight and medical information that defies simple categorization and makes them unique. One such study is the report by Gilbert Rhoton and his colleagues in which they have delineated the basic anatomical relations of the arterial supply to the seventh and eighth cranial nerves in the middle posterior fossa. Apparently these microsurgical interrelationships have never before been described in otological literature as thoroughly as in this essay.

Another major article in this book is the paper by Brian McCabe which presents — also for the first time in the published literature on the subject — the descriptive documentation of the alternations in the facial nerve, distinguishing cases of essential blepharospasm from those of hemifacial spasm so that the latter is pretty well established as a distinct medical entity. A third contribution in this same vein is by Ronald Apfelbaum, who elicits and evaluates the technique for microvascular decompression for hemifacial spasms.

Nevertheless, there are some departures from previous standards that are disagreeable. One such departure is some duplication of previously published material, disguised only by new introductions and slight rearrangements of data published earlier. Another departure from the previous symposia publications is the interdisciplinary orientation that goes beyond the practical neurosurgical concerns of the otolaryngologist. Consequently, in certain respects, the current publication is perhaps less useful for the specialist in otological surgery. Yet, for all that, it may be said that the interdisciplinary breadth and depth are precisely those elements needed to prevent the exclusive viewpoint of the narrow specialist.

This book is an exciting and important new publication. It would be safe to say that anyone who deals with otolaryngology and neurosurgery of the ear will find this work significant in itself and an excellent reference source in the future.

Dennis G. Pappas, MD
Birmingham, Alabama

Diseases of the Ears, Nose and Throat: A Guide to Diagnosis and Management

By *D. Thane Cody*, *Eugene B. Kern* and *Bruce W. Pearson*. Hard cover, black and white illustrations, indexed, 476 pages, 1981. Year Book Medical Publishers, Inc., Chicago.

This book was written to aid the primary care physician in his effort to diagnose and manage the many patients who consult him with otolaryngologic problems. To this end a unique departure from the usual format is used. Much stress is placed upon the patient's symptoms and physical findings, and a systematic differential diagnostic method is presented which is most helpful in arriving at a definite diagnosis. Finally, management of each problem is discussed. A number of tables are used for quick reference by the physician to expedite the diagnostic and therapeutic techniques available. References are understandably few in number, for an amazing fund of information is included, and references are to be found in the standard texts. The illustrations are also few in number, but they are clear and informative.

The need for this book was most apparent, and the authors have risen to the challenge in admirable fashion. It is highly recommended for the primary care physician, but would be equally valuable for the medical student who is serving his/her clinical clerkship in otolaryngology.

G. O. Proud, MD
Kansas City, Kansas

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Send manuscripts by first class mail to Editor Brian F. McCabe, MD, Department of Otolaryngology-Head and Neck Surgery, University of Iowa Hospitals, Iowa City, IA 52242. Original manuscripts which deal with clinical and scientific aspects of otolaryngology, bronchoesophagology, head and neck, maxillofacial and plastic surgery, audiology, speech pathology and related specialties will be considered for publication. It is understood that manuscripts submitted for review have not been published.

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References should be numbered consecutively in the order in which they are first mentioned, cited in the text in arabic numerals and may not exceed 30 in number. Use the style of references given in *Uniform Requirements.** Include in the reference list manuscripts accepted but not yet published; designate the journal followed by "in press" in parentheses. Manuscripts submitted but not yet accepted should be referred to as "unpublished data" in parentheses in the text. Primary references only should be used and must be verified by the author(s) against the original documents. Examples of correct forms of references can be found in current issues of the *Annals.*

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*Ann Intern Med 1982; 96 (Part 1): 766-71.

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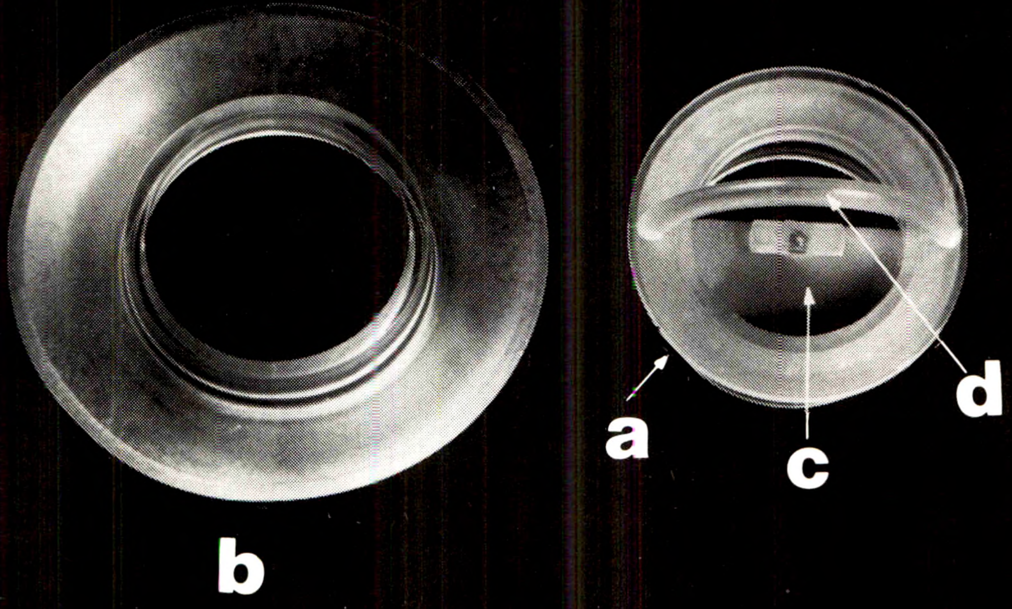

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For further information contact: JoAnn Murdock, Dept. of Otolaryngology-Head & Neck Surgery, University of Iowa Hospitals, Iowa City, Iowa 52242, (319) 356-2797 or (319) 356-3574.

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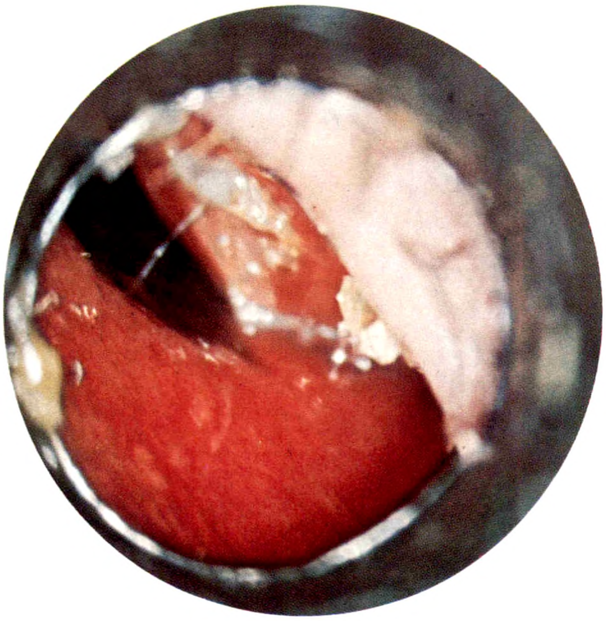
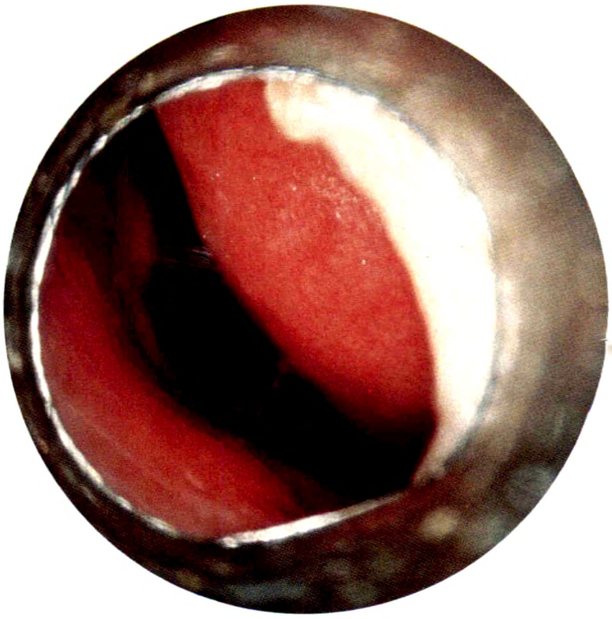


Before Vancenase treatment

Left nostril before VANCENASE Nasal Inhaler treatment:

See marked swelling of turbinate with partially obstructed airway, moderate amount of thin and thickened secretions, red mucosa.



After Vancenase Treatment

Left nostril after using VANCENASE Nasal Inhaler for eight weeks:

Note marked reduction of turbinate size with improvement in nasal patency; minimal secretion, pink (normal) mucosa.

Case history and photograph courtesy of John T. Connell, M.D., Englewood, New Jersey. Dosage was two puffs in each nostril t.i.d. There were no adverse side effects.

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Effective intranasal steroid control with proven safety and convenience

■ Allows freer breathing by direct steroid control of inflamed/boggy nasal mucosa

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The automatic VANCENASE metered-dose aerosol unit assures accurate delivery of safe, minimal quantities of drug for maximum effectiveness and maximum safety. No amounts greater than the recommended dose are administered when simple directions are followed thus precluding the possibility of adrenal suppression.[1]

■ Easy to carry...easy to use

The VANCENASE metered-dose aerosol is small and easy to carry, thus patients can follow your prescribing directions any time of day, in any location, with minimal inconvenience. The simple b.i.d. dosage promotes patient compliance assuring you that your patient's allergic rhinitis is properly controlled.

[*] In those patients poorly responsive to conventional treatment.

[†] Since VANCENASE Nasal Inhaler is not immediately effective, patients should be advised not to increase the dose beyond that prescribed in an effort to obtain a response. Instead, nasal decongestants or oral antihistamines may be needed until the effects of VANCENASE Nasal Inhaler are developed. In some patients, one or two weeks may pass before full relief is obtained. This relief can then be easily maintained with the recommended doses.

[††] When used at recommended dosage. Use of excessive doses of VANCENASE may suppress hypothalamic-pituitary-adrenal function.

[1] Source: Files of Headquarters Medical Research Division, Schering Corporation.

Please see Clinical Considerations section which follows...

In Allergic Rhinitis

Vancenase™ Nasal Inhaler

brand of

beclomethasone dipropionate, USP

Schering

For Nasal Inhalation Only

CLINICAL CONSIDERATIONS:

INDICATIONS AND USAGE VANCENASE Nasal Inhaler is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment.

Clinical studies have shown that improvement is usually apparent within a few days. However, symptomatic relief may not occur in some patients for as long as two weeks. Although systemic effects are minimal at recommended doses, VANCENASE should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE should not be used in the presence of untreated localized infection involving the nasal mucosa.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE Nasal Inhaler can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE Nasal Inhaler, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

PRECAUTIONS **General:** During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE Nasal Inhaler.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE Nasal Inhaler may suppress HPA function.

VANCENASE should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for Patients: Patients should use VANCENASE Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of VANCENASE Nasal Inhaler are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying PATIENT'S INSTRUCTIONS carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95-weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrus cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrus cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with the nasal mucous membranes. Adverse reactions reported in controlled clinical trials and long-term open studies in patients treated with VANCENASE are described below.

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of VANCENASE Nasal Inhaler have been reported. Also, occasional sneezing attacks (10 per 100 patients) have occurred immediately following the use of the intranasal inhaler.

Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely. (See **PRECAUTIONS**.)

Less than 2 per 100 patients reported transient episodes of bloody discharge from the nose.

Ulceration of the nasal mucosa has been reported rarely. Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, i.e., Cushing's syndrome could occur.

DOSAGE AND ADMINISTRATION **Adults and Children 12 years of age and over:** the usual dosage is one inhalation (42 mcg) in each nostril two to four times a day (total dose 168-336 mcg/day). Patients can often be maintained on a maximum dose of one inhalation in each nostril three times a day (252 mcg/day).

In patients who respond to VANCENASE Nasal Inhaler, an improvement of the symptoms of seasonal or perennial rhinitis usually becomes apparent within a few days after the start of VANCENASE Nasal Inhaler therapy.

The therapeutic effects of corticosteroids, unlike those of decongestants are not immediate. This should be explained to the patient in advance in order to ensure cooperation and continuation of treatment with the prescribed dosage regimen.

VANCENASE Nasal Inhaler is not recommended for children below 12 years of age.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of intended action. In such cases it is advisable to use a nasal vasoconstrictor during the first two to three days of VANCENASE Nasal Inhaler therapy.

Directions for Use: Illustrated PATIENT INSTRUCTIONS for proper use accompany each package of VANCENASE Nasal Inhaler.

CONTENTS UNDER PRESSURE. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such symptoms appear, the dosage should be decreased.

The oral LD$_{50}$ of beclomethasone dipropionate is greater than 1 g/kg. One canister of VANCENASE Nasal Inhaler contains 8.4 mg of beclomethasone dipropionate, therefore acute overdosage is unlikely.

HOW SUPPLIED VANCENASE Nasal Inhaler, 16.8 g canister; box of one. Supplied with nasal adapter and PATIENT'S INSTRUCTIONS; (NDC 0085-0041-04).

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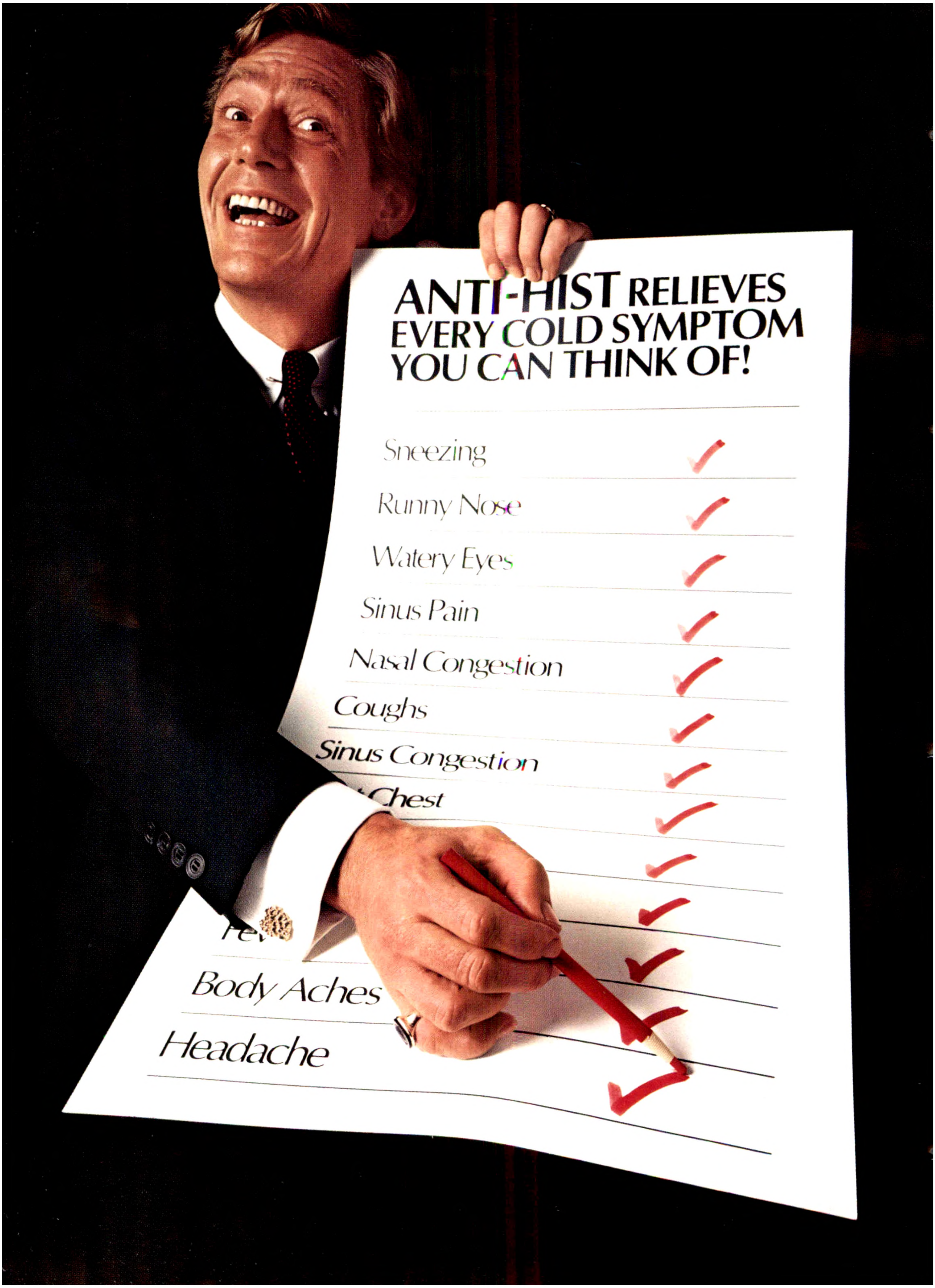
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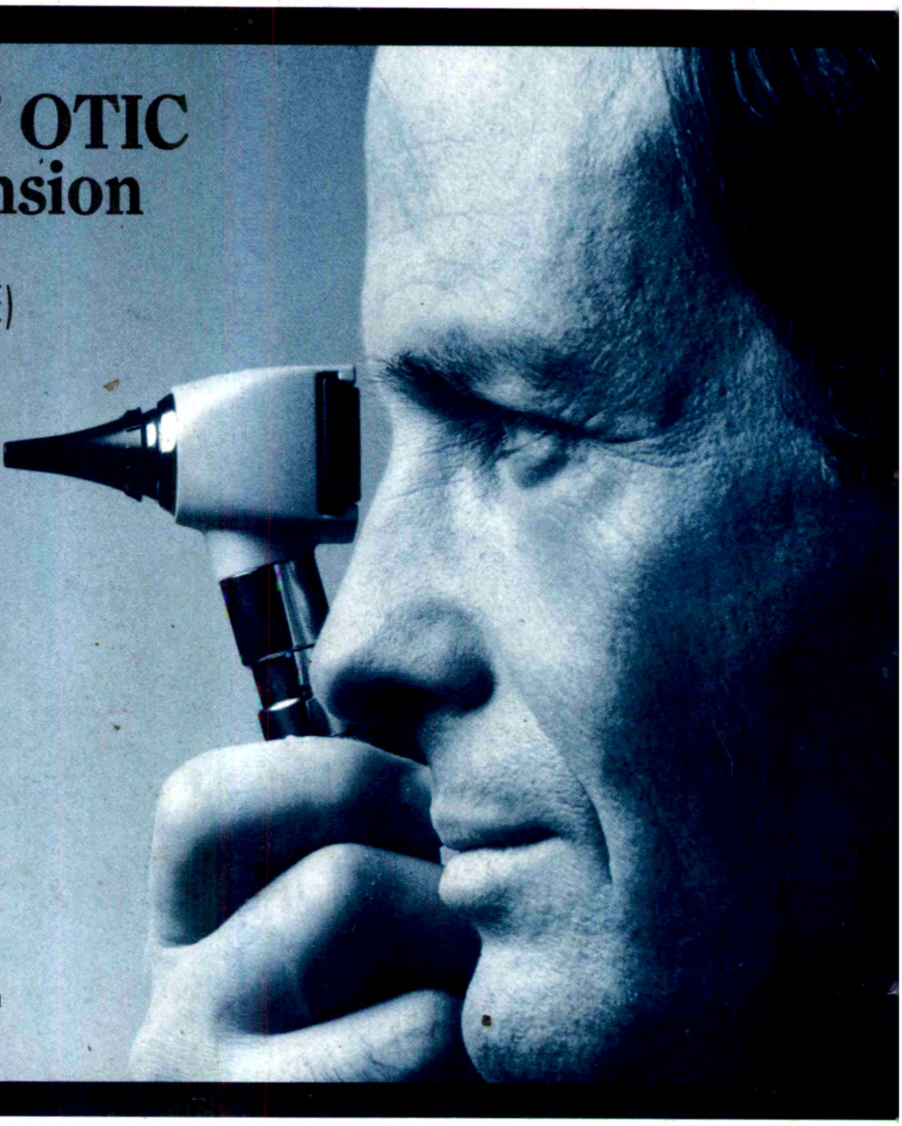

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	Clinical Efficacy
Suspension	
Total ears	93
Responders	91 (97.8%)
Solution	
Total ears	107
Responders	104 (97.2%)
Combined suspension and solution	
Total ears	200
Responders	195 (97.5%)

Adapted from Cassisi et al.[1]

REFERENCE:

1. Cassisi N, Cohn A, Davidson T, et al: Diffuse otitis externa: Clinical and microbiologic findings in the course of a multicenter study on a new otic solution. *Ann Otol Rhinol Laryngol* 86(suppl 39, pt 3):1-16, 1977.

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Indications: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

Precautions: This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

Cortisporin® Otic Solution Sterile (Polymyxin B-Neomycin-Hydrocortisone)
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Indications: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

Precautions: This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

Adverse Reactions: Stinging and burning have been reported when this drug has gained access to the middle ear.

Contraindications, Warnings, Precautions and Adverse Reactions Common to Both Products

Contraindications: These products are contraindicated in those individuals who have shown hypersensitivity to any of the components, and in herpes simplex, vaccinia and varicella.

Warnings: As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

Precautions: If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

Adverse Reactions: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

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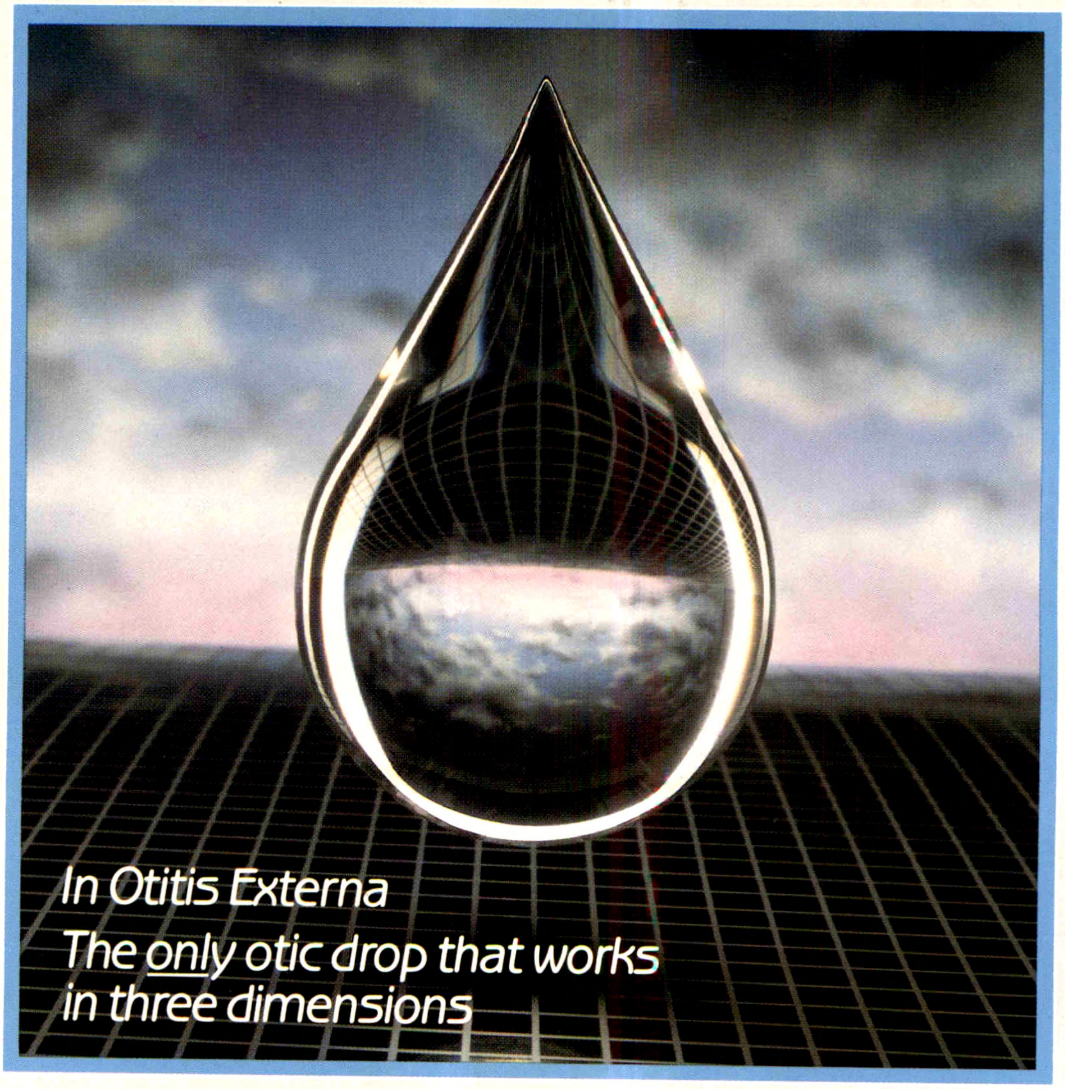
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Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE

For the treatment of superficial bacterial infections of the external auditory canal, caused by organisms susceptible to the action of the antibiotics; and for the treatment of infections of mastoidectomy and fenestration cavities, caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS

This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia and varicella.

WARNINGS

As with other antibiotic preparations, prolonged treatment may result in overgrowth of non-susceptible organisms and fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

PRECAUTIONS
General

If sensitization or irritation occurs, medication should be discontinued promptly.

This drug should be used with care in cases of perforated ear drum and in longstanding cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS

Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

DOSAGE AND ADMINISTRATION

The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator.

For adults, 4 drops of the suspension should be instilled into the affected ear 3 or 4 times daily. For infants and children, 3 drops are suggested because of the smaller capacity of the ear canal.

The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

If preferred, a cotton wick may be inserted into the canal and then the cotton may be saturated with the solution. This wick should be kept moist by adding further solution every 4 hours. The wick should be replaced at least once every 24 hours.

HOW SUPPLIED

Coly-Mycin S Otic is supplied as:
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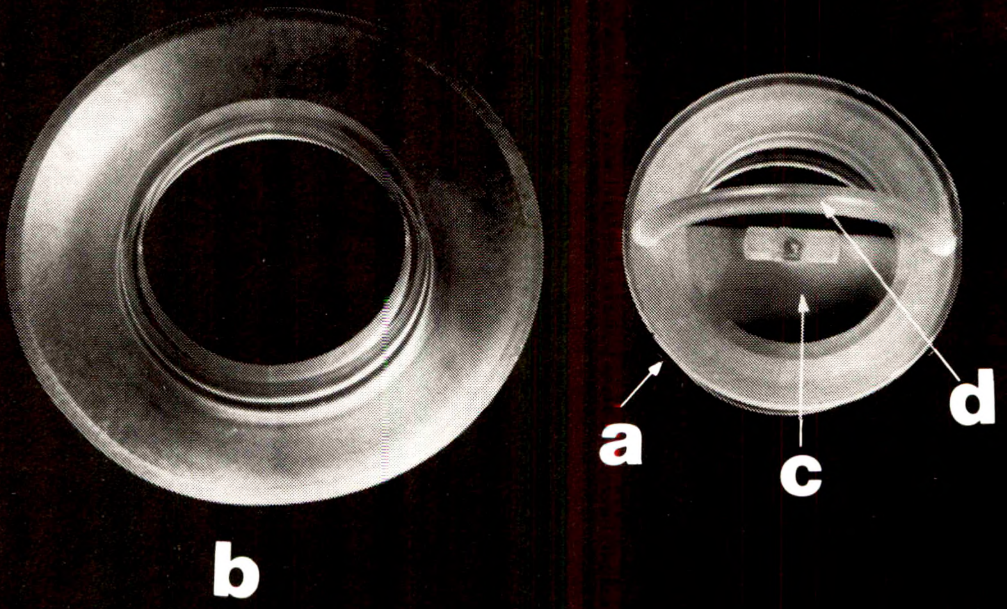

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The 10th annual University of Pittsburgh Symposium on Ear, Nose and Throat Diseases in Children: A 1983 Update will include the most recent results of the Pittsburgh and Boston studies of ear and sinus disease, tonsillectomy, and adenoidectomy.

Otolaryngologists, pediatricians, and other health care professionals — update your knowledge through scientific presentations by the University of Pittsburgh School of Medicine faculty and invited speakers, small-group workshops, and informal discussions. (Simultaneous translation in Spanish available.)

Course Codirectors: Charles D. Bluestone, MD, Jack L. Paradise, MD, and Sylvan E. Stool, MD.

For futher information contact: Dept. of Otolaryngology, Children's Hospital of Pittsburgh, 125 De Soto St, Pittsburgh, PA 15213; (412) 647-5466.

A170

Politzer Society Conference

SURGERY OF THE TEMPORAL BONE

September 11-17, 1983
Montreux, Switzerland

The scientific program will include presentations on temporal bone fractures, disorders of Eustachian tube function, functional repair of sound conductive system, chronic middle ear disease, tumors of the temporal bone, use of the laser in surgery of the temporal bone, immunology in tympanoplasty, heterologous grafting, experiences with gluing and ceramics, and artificial stimulation of the auditory system.

A preliminary list of lecturers includes: W. Arnold, Switzerland; D.F. Austin, USA; P.I. Banfai, Germany; K. Burian, Austria; U.K.R. Charachon, France; C.H. Chouard, France; H. Diamant, Sweden; H. Fisch, Switzerland; J. Helms, Germany; J. Holmquist, Sweden; G. Jako, USA; C.W. Jansen, Germany; E. Kastenbauer, Germany; S. Kubik, Switzerland; E. Marres, Holland; J. Marquet, Belgium; T. McGee, USA; A. Miehlke, Germany; C.R. Pfaltz, Switzerland; D. Plester, Germany; M. Portmann, France; J. Pulec, USA; J. Sadé, Israel; J. Shea, USA; G.D.L. Smyth, Northern Ireland; M.F.W. Smith, USA; Jean-Marc Sterkers, France; A. Sultan, France; J. Thoma, Germany; J. Veldman, Holland; M.E. Wigand, Germany; R.J. Wiet, USA; S. Wullstein, Germany; F. Wustrow, Germany and C. Zini, Italy.

Tuition fee: 600 Swiss Francs ($290) *Payable in Swiss currency.*

Tuition fee includes coffee breaks, lunch at Eurotel, reception at Hotel Eden, night boat tour to France with dinner party, visit of Chillon Castle, classical "belle époque" train tour with lunch to Château d'Oeux and Gruyères and a farewell dinner party at a famous mountain farmhouse.

Excellent hotel accommodations available from 70 Swiss Francs ($35) to 185 Swiss Francs($90).

Registration deadline: August 15, 1983.

For application and further details of the program contact: Dr. C. W. Jansen, Conference Secretary, Winterbeckestrasse 11, 5270 Gummersback, West Germany.

For hotel reservations and travel arrangements contact: William Muller, Steinenvorstadt 33, CH-4002 Basle, Switzerland.

A169

The new GSI 10 microprocessor-based audiometer.

One of its most impressive features is the Grason-Stadler label.

A small suggestion for buying new technology.

Before you select a microprocessor-based audiometer, look at the reputation of the people who build it.

For example, ask audiologists and otologists about Grason-Stadler audiometers. For years, we've built instruments with great diagnostic capability and unfailing reliability.

The GSI 10 microprocessor-based audiometer is our latest and most powerful.

IT'S A COMPLETE DIAGNOSTIC LABORATORY

The GSI 10 offers all of the capability of our 1701 and a whole lot more. Here's just a few of its new functions.

- Automated Hughson-Westlake procedure.
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- Tone and masking intensity tracking.
- Dual frequency for MLB tests.
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- A running timer for tone decay testing.
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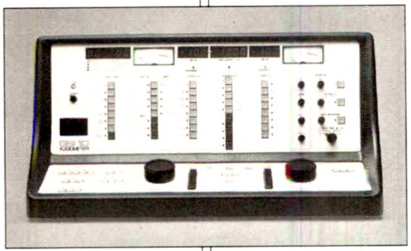
- Auxiliary intercom for test room assistant

There's more. Get our GSI 10 brochure for a complete listing.



IT'S EASY TO USE.

Watch your patient and let your fingers do the walking. Frequency, intensity, present stimulus and other "test execute" knobs and built-in detent, you can even increase stimulus intensity without looking at the HL dial.

And should you ever need to look, frequency and intensity LED display are at the top of the instrument, right at eye level.

IT'LL KEEP GOING.

Time is money.

When an audiometer breaks down, patient scheduling backs up. Expensive personnel are left sitting around. A busy clinic needs its audiometer on line every day.

With Grason-Stadler, you never need to worry. Our audiometers have a reputation for being dependable and trouble-free.

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THERE'S 33 SERVICE CENTERS NATION-WIDE.

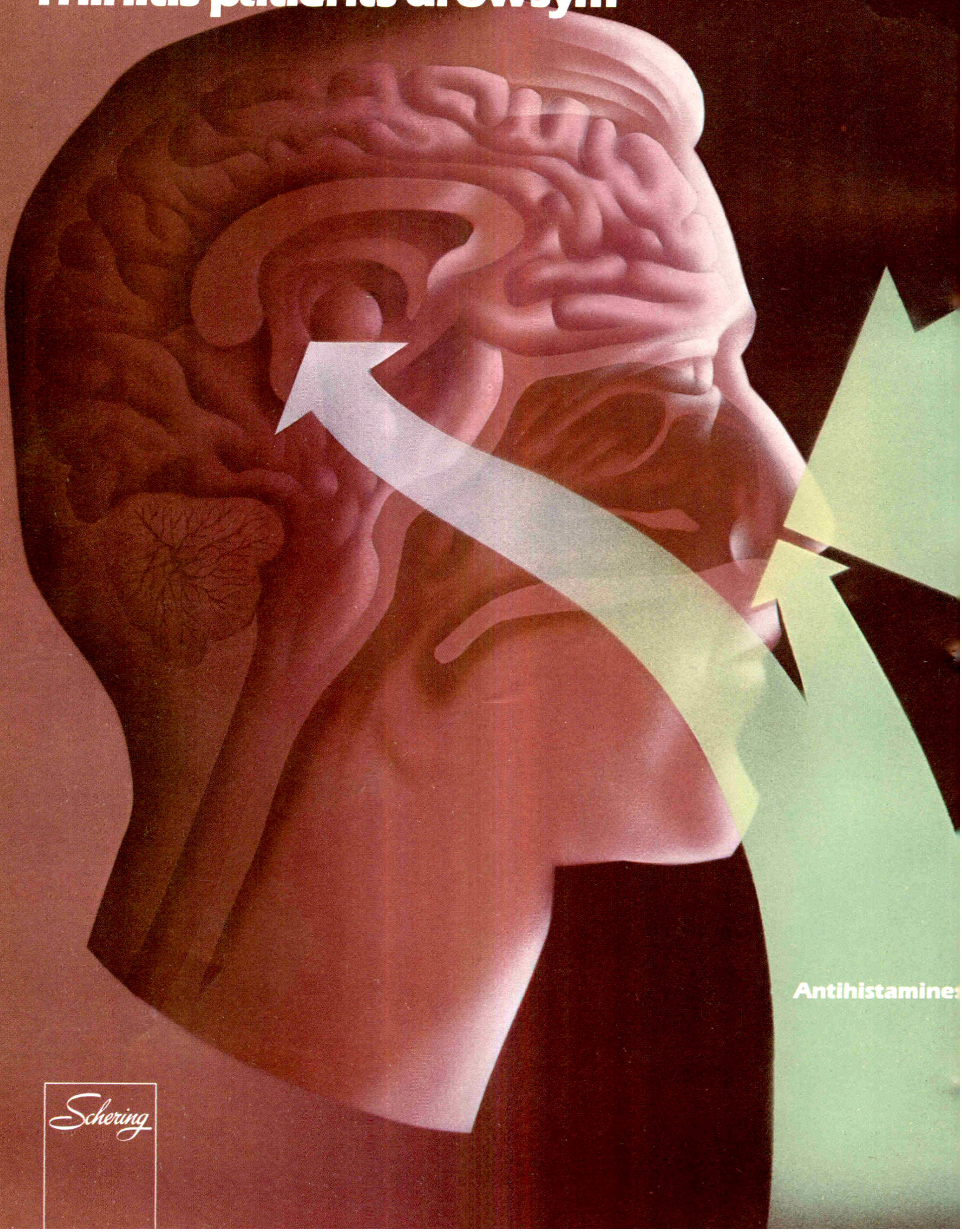
The GSI 10 features modular (PC board) construction and an easy troubleshooting routine. Should your GSI 10 microprocessor-based audiometer fail, we can have it back in operation within 48 hours.

CALL FOR A FREE DEMONSTRATION.

See the GSI 10 for yourself. For a demonstration, contact Grason-Stadler, Inc., 537 Great Road, Littleton, MA 01460, (617) 486-3514.

Grason-Stadler, Inc.

When antihistamines make rhinitis patients drowsy...



Avoid drowsiness with site-targeted therapy

VANCENASE™ Nasal Inhaler

brand of beclomethasone dipropionate, USP

A valuable alternative when conventional therapy fails

Spares patients the CNS effects of antihistamines

VANCENASE™ offers an attractive alternative to antihistamines when drowsiness compromises therapeutic results in seasonal or perennial rhinitis. Because it acts directly on the nasal mucosa and exhibits no central action, VANCENASE does not affect mental alertness.

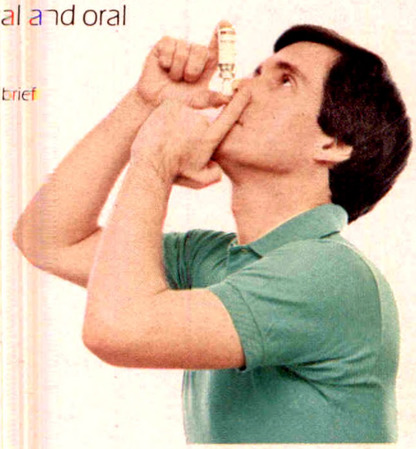
Does not impair adrenal function at therapeutic dosages

In clinical studies using beclomethasone dipropionate intranasally, there was no evidence of adrenal insufficiency.

Provides a solution to rebound congestion

VANCENASE avoids this troublesome problem associated with the use of topical and oral decongestants.

Please see next page for brief summary of prescribing information.



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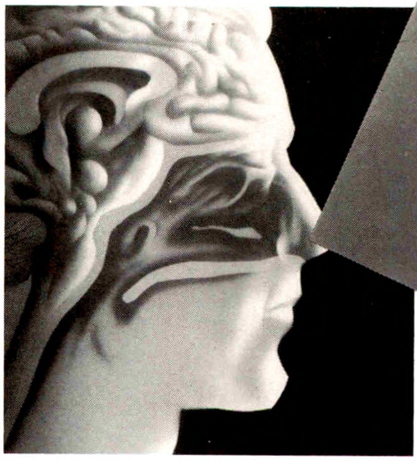
When antihistamines make rhinitis patients drowsy —



VANCENASE™ Nasal Inhaler

brand of beclomethasone dipropionate, USP

For Nasal Inhalation Only

CLINICAL CONSIDERATIONS

INDICATIONS AND USAGE: VANCENASE Nasal Inhaler is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment.

Clinical studies have shown that improvement is usually apparent within a few days. However, symptomatic relief may not occur in some patients for as long as two weeks. Although systemic effects are minimal at recommended doses, VANCENASE should not be continued beyond three weeks in the absence of significant symptomatic improvement. VANCENASE should not be used in the presence of untreated localized infection involving the nasal mucosa.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with VANCENASE Nasal Inhaler can be accompanied by signs of adrenal insufficiency.

When transferred to VANCENASE Nasal Inhaler, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate day prednisone systemic treatment and orally inhaled beclomethasone increased the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, VANCENASE treatment should be used with caution in patients already on alternate day prednisone regimens for any disease.

PRECAUTIONS General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with Candida albicans has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with VANCENASE Nasal Inhaler.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of VANCENASE Nasal Inhaler may suppress HPA function.

VANCENASE should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for Patients: Patients should use VANCENASE Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of VANCENASE Nasal Inhaler are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying PATIENT'S INSTRUCTIONS carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95-weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrus cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrus cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy Category C: Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when VANCENASE Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with the nasal mucous membranes. Adverse reactions reported in controlled clinical trials and long-term open studies in patients treated with VANCENASE are described below.

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of VANCENASE Nasal Inhaler have been reported. Also, occasional sneezing attacks (10 per 100 patients) have occurred immediately following the use of the intranasal inhaler.

Localized infections of the nose and pharynx with Candida albicans have occurred rarely. (See PRECAUTIONS.)

Less than 2 per 100 patients reported transient episodes of bloody discharge from the nose.

Ulceration of the nasal mucosa has been reported rarely. Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, i.e., Cushing's syndrome could occur.

DOSAGE AND ADMINISTRATION Adults and Children 12 years of age and over: the usual dosage is one inhalation (42 mcg) in each nostril two to four times a day (total dose 168-336 mcg/day). Patients can often be maintained on a maximum dose of one inhalation in each nostril three times a day (252 mcg/day).

In patients who respond to VANCENASE Nasal Inhaler, an improvement of the symptoms of seasonal or perennial rhinitis usually becomes apparent within a few days after the start of VANCENASE Nasal Inhaler therapy.

The therapeutic effects of corticosteroids, unlike those of decongestants are not immediate. This should be explained to the patient in advance in order to ensure cooperation and continuation of treatment with the prescribed dosage regimen.

VANCENASE Nasal Inhaler is not recommended for children below 12 years of age.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of intended action. In such cases it is advisable to use a nasal vasoconstrictor during the first two to three days of VANCENASE Nasal Inhaler therapy.

Directions for Use: Illustrated PATIENT INSTRUCTIONS for proper use accompany each package of VANCENASE Nasal Inhaler.

CONTENTS UNDER PRESSURE. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such symptoms appear, the dosage should be decreased.

The oral LD_{50} of beclomethasone dipropionate is greater than 1 g/kg in rodents. One canister of VANCENASE Nasal Inhaler contains 8.4 mg of beclomethasone dipropionate, therefore acute overdosage is unlikely.

HOW SUPPLIED VANCENASE Nasal Inhaler, 16.8 g canister; box of one. Supplied with nasal adapter and PATIENT'S INSTRUCTIONS; (NDC 0085-0041-04).

Store between 2° and 30°C (36° and 86°F).

Manufactured by Aerosol Techniques, Inc., Armstrong Laboratories Division, West Roxbury, MA 02123 for Schering Corporation, Kenilworth, N.J. 07033.

For more complete details, consult package insert or Schering literature available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

C-12381913 Revised 9/81
1459-8404

Schering

Schering Corporation
Kenilworth, New Jersey 07033

New COCAINE HYDROCHLORIDE TOPICAL SOLUTION CII

(Not For Injection or Ophthalmic Use)

Here at last, commercially prepared Cocaine HCl Topical Solutions to relieve you from an onerous and sensitive compounding task.

5x4 ml
10% COCAINE HYDROCHLORIDE CII
TOPICAL SOLUTION
(WARNING: May be habit forming)
Roxane Laboratories, Inc. Columbus, Ohio 43216
Each ml contains: Cocaine Hydrochloride 100 mg
(WARNING: May be habit forming)
See Package Insert for Complete Prescribing Information
Store at Controlled Room Temperature 15°-30° (59°-86°F)
Keep in a secure area and protect from diversion
Caution: Federal law prohibits dispensing without prescription
NDC 0054-8151-03
COCAINE HYDROCHLORIDE 10% CII
Topical Solution
(WARNING: May be habit forming)
NOT FOR OPHTHALMIC USE
5 x 4 ml
062
4 ml COCAINE HYDROCHLORIDE CII TOPICAL 10% SOLUTION
10%
10%/4ml
NDC 0054-8151
4 ml
COCAINE HYDROCHLORIDE CII
TOPICAL 10% SOLUTION
PEEL
NDC 0054-8150
4 ml
COCAINE HYDROCHLORIDE CII
TOPICAL 4% SOLUTION
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Ready For Use

Roxane Laboratories leadership in Unit Dose packaged liquid formulations is extended to Cocaine HCl Topical Solution. This pale blue-green formulation is proven stable and fully potent to the expiration date printed on each cup lid. This is particularly important for a product with known stability problems.

The advantages of a commercially prepared Unit Dose product are well established.

- The product is clearly and consistently labeled.
- Control is maximized when only the amount needed for each procedure is delivered to the nurse or physician.
- Any unopened cups can be returned to inventory.

To Order Cocaine Hydrochloride Topical Solution, simply fill out your DEA Form 222 and purchase order as follows:

Mail the order to:
Roxane Laboratories, Inc.
P.O. 16532
Columbus, OH 43216

Size of Package	Name of Item	National Drug Code	Price
5x4ml	Cocaine HCl 4%	0054-8150-03	$32.50
5x4ml	Cocaine HCl 10%	0054-8151-03	$45.00

A $10.00 handling charge will be waived if the total order for Schedule II products amounts to $75.00 or more.

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Columbus, Ohio 43216

OUR FIFTEENTH YEAR OF UNIT DOSE LEADERSHIP

ROXANE LABORATORIES, INC

COCAINE HYDROCHLORIDE TOPICAL SOLUTION CII

INDICATIONS AND USAGE

Cocaine Hydrochloride Topical Solution is indicated for the introduction of local (topical) anesthesia of accessible mucous membranes of the oral, laryngeal and nasal cavities.

CONTRAINDICATIONS

Cocaine Hydrochloride is contraindicated in patients with a known history of hypersensitivity to the drug or to the components of the topical solution.

WARNINGS

RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Carcinogenesis, Mutagenesis: Long-term studies to determine the carcinogenic and mutagenic potential of cocaine are not available.

PRECAUTIONS

The safety and effectiveness of Cocaine Hydrochloride Topical Solution depends on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status.

Cocaine Hydrochloride Topical Solution should be used with caution in patients with severely traumatized mucosa and sepsis in the region of the proposed application. Use with caution in persons with known drug sensitivities.

ADVERSE REACTIONS

Adverse reactions may be due to high plasma levels as a result of excessive and rapid absorption of the drug. Reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, restlessness and excitement. Tremors and eventually clonic-tonic convulsions may result. Emesis may occur. Central stimulation is followed by depression, with death resulting from respiratory failure.

Small doses of cocaine slow the heart rate, but after moderate doses, the rate is increased due to central sympathetic stimulation.

Cocaine is pyrogenic, augmenting heat production in stimulating muscular activity and causing vasoconstriction which decreases heat loss. Cocaine is known to interfere with the uptake of norepinephrine by adrenergic nerve terminals, producing sensitization to catecholamines, causing vasoconstriction and mydriasis.

Cocaine causes sloughing of the corneal epithelium, causing clouding, pitting, and occasionally ulceration of the cornea. The drug is not meant for ophthalmic use.

HOW SUPPLIED

4% Cocaine Hydrochloride Topical Solution
NDC 0054-8150-03: Unit dose Patient Cup™ filled to contain 4 ml, five 4 ml Patient Cups™ per carton.
10% Cocaine Hydrochloride Topical Solution
NDC 0054-8151-03: Unit dose Patient Cup™ filled to contain 4 ml, five 4 ml Patient Cups™ per carton.

Store at Controlled Room Temperature
15°-30°C (59°-86°F)

Caution: Federal law prohibits dispensing without prescription.

Issued August 1982

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Columbus, Ohio 43216

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Sixteen physician multispecialty and family physician group in southern Wisconsin is seeking a board eligible otolaryngologist. Excellent practice opportunity and very competitive starting salary and benefits. Eligible to become full shareholder after one year. Easy access to metropolitan areas of Milwaukee and Madison, Wisconsin.

Please send CV or call:
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A163

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Department of Otolaryngology
Henry Ford Hospital
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FELLOWSHIP
IN
HEAD AND NECK SURGERY

University of Iowa

A one- to two-year fellowship is being offered by the University of Iowa, Department of Otolaryngology-Head and Neck Surgery, Division of Head and Neck Surgery. The fellowship consists of active involvement in the management of all aspects of oncologic, plastic and reconstructive surgery of the head and neck. Teaching and research are also required. Candidates must be able to obtain an Iowa medical license.

The University of Iowa is an equal opportunity/affirmative action employer.

For further information contact:
William R. Panje, MD
Dept. of Otolaryngology-Head & Neck Surgery
University of Iowa
Iowa City, Iowa 52242
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Remarkably Simple.

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All tests are performed automatically and rapidly, allowing more effective use of professional time. Results are printed on an IBM sized card for easy filing.

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Telephone: (02) 946000
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A great place to live, play, and practice medicine, located approximately 42 miles northeast of Charlotte. County has population base of 48,000 and has excellent living conditions, recreational facilities, and educational systems.

Community completed and occupied in the spring of 1981 a new 130-bed, all private room, replacement hospital with a 29-member medical staff representing the specialties of family practice, internal medicine, urology, general surgery, radiology, pediatrics, obstetrics and gynecology, pathology, opthalmology, and orthopedic and hand surgery.

For further information send curriculum vitae to: Mr. Donald B. Logan, Stanly Memorial Hospital, Inc., P. O. Box 1489, Albemarle, NC 28001. A148

TEMPORAL BONE SURGICAL DISSECTION COURSES

Department of Otorhinolaryngology
University of Michigan Medical School
Malcolm D. Graham, MD, Course Director

Sept. 12-16, 1983; Sept. 26-30, 1983;
Oct. 31-Nov. 4, 1983; Nov. 14-18, 1983

Intensive one-week courses emphasize the surgical and anatomical approaches to temporal bone and are presented in a manner relevant for the otologic surgeon, utilizing lectures, videotape presentations of surgical techniques and temporal bone dissection.

Mornings and afternoons are spent in the dissection laboratory giving extensive drilling experience in both temporal bone anatomy and surgical techniques. Lectures and demonstrations provided by faculty of the Dept. of Otorhinolaryngology and Kresge Hearing Research Institute, blending basic science and clinical otologic instruction. Dissection instruments will be provided.

FEE — $1000

50 Hours Category I CME Credits

For further information contact: Malcolm D. Graham, MD, Dept. of Otorhinolaryngology, University of Michigan Medical Center, Ann Arbor, MI 48109, (313) 764-4131 or (313) 764-8110.

A45

RESEARCH SCIENTIST

The Denver Center for the Performing Arts has founded a research laboratory, in Denver, for the study of laryngeal and respiratory function, both as basic research and in application to vocal performance. The Director is Dr. Wilbur J. Gould and the Associate Director, as consultant, is Dr. Ingo R. Titze.

Responsibilities include developing and carrying out research program in voice area, developing a laboratory, grant writing, cooperation with visiting scientists; emphasis on voice physiology, acoustics, or perception. Must have demonstrated ability to design and report research; background in physical or biological sciences, engineering, medicine, experimental phonetics/speech science, or research in vocal performance. Should have interest in vocal arts and enhancement of vocal performance in both live and recorded form. Starting salary approximately $27,500, depending on qualifications.

Send letter of application with CV, bibliography, and three or more letters of recommendation to: **Dr. Ingo R. Titze**, Department of Speech Pathology and Audiology, University of Iowa, Iowa City, IA 52242.

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OTOLARYNGOLOGIST

HEAD AND NECK SURGEON

The Department of Surgery at Kern Medical Center in Bakersfield, California, seeks an otolaryngologist/head and neck surgeon for geographic full-time practice. The department is an academic affiliate of the Department of Surgery and its Division of Otolaryngology/Head & Neck Surgery of the UCSD School of Medicine, San Diego, California.

Qualifications include board certification, a strong interest in teaching and a broad background of clinical skills including experience in facial trauma, adult and pediatric endoscopy and head and neck cancer. The position offers an opportunity to participate in a private practice plan and includes a faculty appointment in the Division of Head and Neck Surgery, UCSD School of Medicine, with rank commensurate with qualifications and experience.

Interested candidates should send a curriculum vitae to: Jack H. Bloch, MD, Chairman, Department of Surgery, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305.

A168

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Sudafed® S.A.
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SUSTAINED ACTION NASAL DECONGESTANT
UP TO 12 HOUR TEMPORARY RELIEF OF NASAL CONGESTION... HELPS DECONGEST SINUS OPENINGS, SINUS PASSAGES
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relieves nasal and sinus congestion without drowsiness
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Sudafed® S.A.
(pseudoephedrine HCl) 120 mg capsules

Sustained action for potent 12-hour relief

Not recommended for children under 12 years of age

Available without Rx in packages of 10s and 40s

And remember the rest of the family...

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Sudafed® Syrup
(pseudoephedrine HCl), a tasty raspberry-flavored syrup containing 30 mg per 5 cc

Sudafed® Cough Syrup
(pseudoephedrine HCl) containing 30 mg per 5 cc

Potent relief without drowsiness

Wellcome

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North Carolina 27709

Stuck?

Are you stuck? It frequently happens with a difficult case. You have a series of test results, but definitive information is missing.

You can acquire missing information in many of your most difficult cases with the NICOLET PATHFINDER II. Comprehensive electrodiagnostic capability for evaluating auditory sensitivity, neural integrity, and cognitive processing is now available in a single top quality instrument.

Anything less than top quality evoked potential instrumentation can leave you stuck with unreliable data and a backlog of patients waiting to be tested. The NICOLET PATHFINDER II provides complete, high-quality data faster. Cost effectiveness is increased because more patients can be tested each day.

Anything less than top quality evoked potential instrumentation can leave you stuck with an inflexible system that quickly becomes obsolete. Flexibility is a major feature of the NICOLET PATHFINDER II. The modular design and software control guarantee the long-life of the system. Extended life of the system means increased cost effectiveness.

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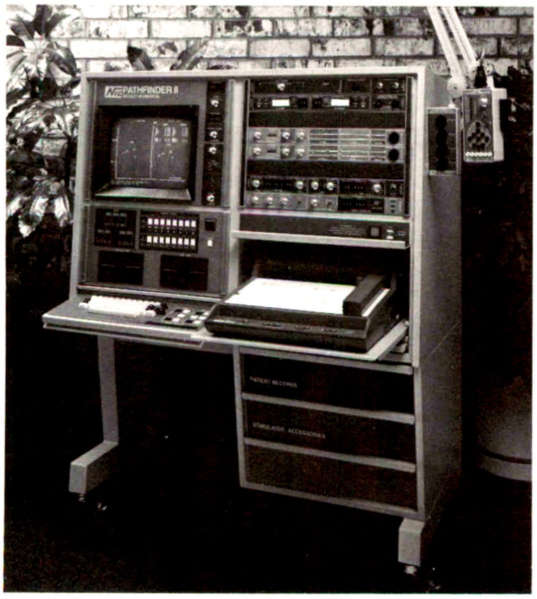

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Ann Otol Rhinol Laryngol 92:1983

FUNCTIONAL NECK DISSECTION

ANATOMICAL GROUNDS, SURGICAL TECHNIQUE, CLINICAL OBSERVATIONS

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The anatomical grounds of and surgical technique for functional neck dissection are described in detail in order to demonstrate that the radicalism of this procedure, from the viewpoint of surgical anatomy, is by no means less than that of the classical (so-called radical) neck dissection. From 1972 to 1978, 476 operations were performed (211 patients treated bilaterally and 54 unilaterally). The percentage of false negatives (ie, histologically proven metastases in clinically unsuspected nodes) was 14%, while the percentage of false positives (histological negativity in clinically suspected nodes) reached 53%. The total number of local recurrences in a three-year follow-up was nine (3.5%).

Surgical treatment of metastatic cancer of the neck, which since the beginning of this century was based invariably on the neck dissection described by Crile,[1] was revolutionized in the 1960s by the introduction of a new procedure which Bocca[2] named "functional neck dissection" (FND). The rationale for this approach is that radical removal of the contents of the spaces where lymph nodes are included may be equally effective if the fasciae enveloping these spaces are wholly elevated and excised. The sternomastoid muscle and the internal jugular vein, which actually lie outside the spaces, can therefore be spared when they are not directly invaded. Furthermore, the precautionary isolation of important nerve trunks, such as the hypoglossus, spinal accessory, and phrenic, makes it possible to avoid any unnecessary functional deficit.

A number of reports[3-6] have demonstrated from a statistical viewpoint that FND is as safe as the classical neck dissection in the treatment of N0-N1 cases. In spite of this and of the remarkable advantages of the procedure, which were recently fully covered by Bocca et al,[7,8] FND is facing great obstacles to its acceptance, even though the common trend of modern surgery fosters functional preservation. There are probably several reasons for this difficulty. One of them, in our opinion, is that up to now the various descriptions of the operative technique did not thoroughly elucidate the anatomical grounds for FND and therefore failed to demonstrate, from the viewpoint of surgical anatomy, the full radicalism of the procedure.

ANATOMY

The basic principle of FND, enunciated by Suarez[9] and confirmed by investigations performed in our department,[10] states that there are no lymph nodes within the fascial wrappings which bind the muscles, nor within the carotid sheath. (It must be stressed, however, that lymph nodes often lie very close to the fasciae; these can be safely elevated only in the absence of any infiltrative growth beyond the capsule.) In order to remove the lymph nodes, the spaces where they dwell must be completely emptied, starting by elevating their "wrapping cloths."

To attain this end, it is obviously necessary to be familiar with every anatomic boundary of the spaces; an arbitrary limit can be set only when an actual anatomic boundary is lacking. In our opinion, the topography of the neck which best fits the requirements of FND is that of the Viennese anatomist, Pernkopf.[11] According to this author, only two fasciae are encountered in the neck: a) the outer fascia, which invests the muscles of branchial origin (sternomastoid and trapezius); and b) the inner fascia, which wraps the autochthonous muscles, ie, those originating from the cervical myotomi (system of the scaleni; system of the recti or strap muscles; system of the prevertebral muscles).

The outer fascia (Fig 1A) covers the surface of the neck like a muff, just below the platysma. It splits into two layers as it invests the sternomastoid; it blends with the inner fascia ventrally, along the midline.

The inner fascia anteriorly wraps the strap muscles and then is broken in the gap between the sternothyroid and anterior scalene muscles. This opening, called the anterior scalenic niche, is actually filled by a sheath of vascular origin, the carotid sheath. The inner fascia then covers the prevertebral muscles, the scalenes, the levator muscle of the scapula, and investing the splenius extends up to the nape. In the interval between the anterior and middle scalenes the inner fascia shows a second small gap, the posterior scalenic niche, which is crossed by the brachial plexus.

Thus we find two main spaces in the neck, the *central* and the *lateral*, which are separated by the carotid sheath fastened in the anterior scalenic

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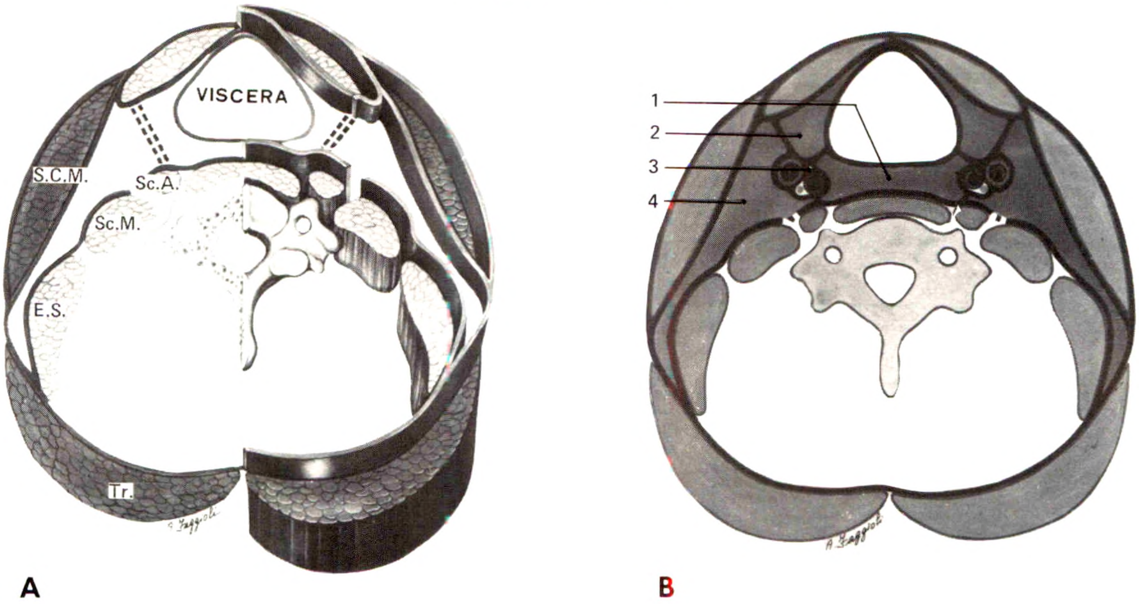

Fig 1. Schematic cross section of neck showing A) arrangement of two cervical fasciae. Outer fascia wraps branchial muscles, sternomastoid (S.C.M.) and trapezius (Tr.), while inner fascia covers autochthonous muscles; among them are shown anterior and middle scalene muscles (Sc. A. and Sc. M., respectively) and levator muscle of scapula (E.S.). There is an interruption in inner fascia between sternothyroid and anterior scalene muscles (broken lines) which is actually filled by aponeurosis of vascular origin, carotid sheath. B) 1 — Retrovisceral (prevertebral) space; 2 — Paravisceral space; 3 — Carotid sheath; 4 — Lateral space. Note that retrovisceral and paravisceral spaces are separated by partition which connects carotid sheath to viscera. This is called sagittal aponeurosis and acts like mesentery, carrying blood vessels to viscera.

niche (Fig 1B). While the lateral space consists of a single chamber, the central space is further divided into several compartments: the visceral space, enveloped by the sheath which covers the laryngeal and pharyngeal muscles; and the paravisceral space, bilateral, which the carotid sheath separates from the lateral space. Another aponeurosis of vascular origin, the sagittal aponeurosis, divides it from the retrovisceral (prevertebral) space.

The spaces which must be emptied during FND are the lateral and the paravisceral. Both are in the shape of pyramids; however, the paravisceral space is inverted. The partition wall between them is the carotid sheath (Fig 2).

The *lateral space* has a cranial apex, which abuts on the temporal bone, and a caudal base. At the bottom there is no actual anatomic boundary as the space merges into the axilla through the cervico-axillary canal. An arbitrary boundary must, therefore, be set up here at the clavicle level.

The horizontal section of the space is quasitriangular (Fig 1B). The medial side is the carotid sheath, the posterior side is the inner fascia covering the scaleni muscles and the levator muscle of the scapula. On the lateral side we find the outer fascia, which upward and forward underlies the sternomastoid and downward and backward is fastened between the sternomastoid and trapezius. It follows that only a part of the lateral space directly faces the outside and corresponds to the posterior neck triangle. The other part, which is covered by the sternomastoid, is called the submuscular recess.

Dorsally, the submuscular recess ends at the posterior border of the levator muscle of the scapula. Hence, the two fascial layers, one underlying the sternomastoid and the other overlying the splenius, blend together.[10] Therefore, the posterior border of the levator muscle of the scapula represents the posterior limit of the dissection in the upper part of the neck.

The *carotid sheath* is a sheet of dense collagen fibers with a central bulge where the carotid arteries and the vagus and sympathetic nerves are embedded. The internal jugular vein, on the contrary, is not included in the sheet, but is in a lateral extension joined to the septum by a thin isthmus. As lymph nodes often creep into the interstices between the jugular expansion and the main sheet, the vein must be skeletonized around its whole circumference, if one decides to preserve it.

The *paravisceral space* has the apex facing caudad, on the level of the lateral thyroid lobe; its base, facing cephalad, has no real anatomic boundary as it merges into the parapharyngeal space of the head where the sagittal aponeurosis of the neck becomes the thick fibromuscular stylopharyngeal septum. An arbitrary limit must therefore be set up corresponding to the posterior belly of the digastric muscle. The section of this space is again in the shape of a triangle. Its ventral side is formed by the inner fascia underlying the strap muscles; backward, the lateral side is the carotid sheath, while the visceral fascia and the sagittal aponeurosis form the medial side (Fig 1B).

STRATEGY OF THE OPERATION

In our opinion, the greatest difficulty encountered by those who start applying the technique of FND is to grasp the strategy of the operation. As a preliminary subdivision, we can distinguish the following steps: dissection of the lateral space; dissection of the carotid sheath; and dissection of the paravisceral space. While the last two are easy to describe, the first is complicated by the peculiar arrangement of the lateral space which has one part, the posterior triangle, directly accessible after the skin has been elevated, and another part, the submuscular recess, which is covered by the sternomastoid muscle.

The submuscular recess can be reached only by passing in front of (medially to) the sternomastoid. Once the dissection of the recess is finished, one has to move backward, behind (laterally to) the sternomastoid, in order to dissect the posterior triangle. The contents of the recess must, therefore, be slid under the sternomastoid and conveyed into the posterior triangle. This is one of the characteristic "sliding maneuvers" of FND under the structures to be preserved. The continuity of the surgical specimen is very firm and holds up against vigorous pulls as the tissues are everywhere enwrapped by the fasciae which are gradually elevated from the underlying planes.

In the posterior triangle, the spinal accessory nerve divides the space into a cranial (supraspinal) and a caudal (subspinal) half. If the nerve can be spared, it is isolated along its whole path. Then the block of the supraspinal dissection is slid under the nerve and carried into the caudal part.

When the lateral space has been completely emptied, the dissection of the carotid sheath begins. In this regard, one must recall that in the paravisceral space the distance from top to bottom is less than in the lateral space. It follows that the cranial and caudal ends of the carotid sheath do not border on the paravisceral space but rather on the parapharyngeal space of the head and on the thyroid gland, respectively. In both sites, one confines oneself to the elevation of the fascia from the lateral aspect of the sheath. However, in the length which is common to both the lateral and the paravisceral space, the sheath is completely dissected, thus making it possible to reach the paravisceral space without breaking the continuity of the fasciae. At the end, a single cavity is present in the neck, including the lateral and paravisceral spaces, with a jutting spur between them, which is the residue of the carotid sheath (Fig 3).

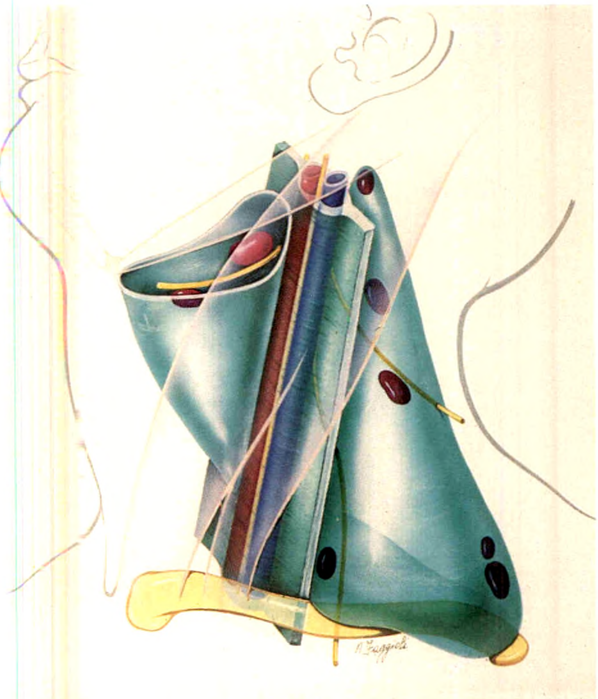

Fig 2. Schematic of neck showing lateral and paravisceral spaces which must be dissected during operation. Both contain lymph nodes and nerve trunks; they are separated by carotid sheath. Inferior limit of lateral space is set up at clavicle level, while upper limit of paravisceral space is set up at level of digastric muscle, (transparent). Sternomastoid muscle, (also transparent), covers most cranial part of lateral space, viz, submuscular recess, while lowest part of same space, corresponding to posterior neck triangle, directly faces outside.

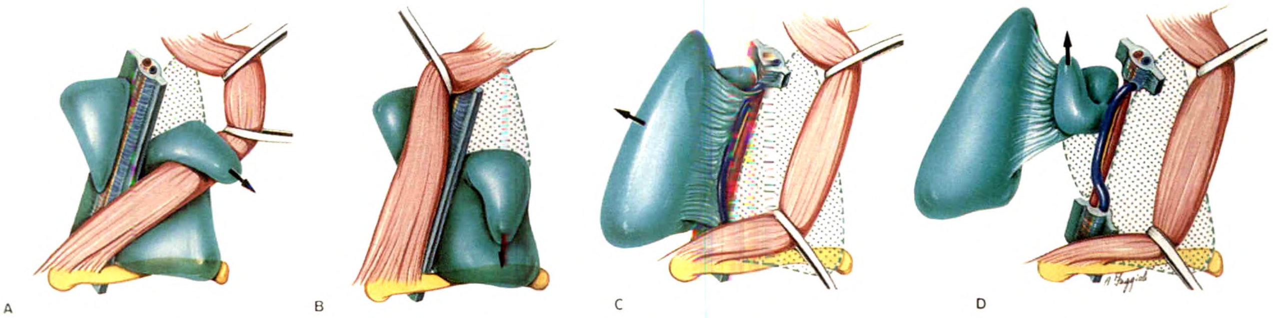

Fig 3. Surgical steps of FND. A) Starting from its apex, submuscular recess of lateral space is dissected. B) Content of submuscular recess has been slid under sternomastoid. Now posterior neck triangle is dissected. C) As dissection of lateral space is accomplished, dissection of carotid sheath is begun. D) Dissection of paravisceral space from caudad to cephalad is final step.

The actual surgical steps are the following:[12]

1. preparation of the surgical field and incision of the outer cervical fascia;
2. dissection of the lateral space, consisting of a) dissection of the submuscular recess; b) preparation of the posterior triangle (isolation of the spinal accessory nerve); and c) dissection of the supraspinal and subspinal parts of the posterior triangle;
3. dissection of the carotid sheath;
4. dissection of the paravisceral space;

Each space is dissected from top to bottom, ie, from cephalad to caudad for the lateral space and from caudad to cephalad from the paravisceral space. The dissection of the carotid sheath marks the passage from one space to the other.

SURGICAL TECHNIQUE

PREPARATION OF THE SURGICAL FIELD AND INCISION OF THE OUTER CERVICAL FASCIA

Skin and platysma muscle are elevated from the outer fascia. The surgical field extends from the thyroid cartilage to the anterior border of the trapezius and from the clavicle to the mandible and mastoid.

The external jugular vein is ligated at the inferior parotid pole which is excised in order to ensure the removal of the lymph node(s) at the inferior border of the gland. A second ligature is carried out in the fossa ovalis, that is, where the vein pierces the fascia. The fascia is then interrupted with two incision lines, the first roughly dividing the outer aspect of the sternomastoid into a medial and lateral half, the second, which runs perpendicularly to the former, starting from the anterior border of the sternomastoid and reaching the surface of the submandibular gland (Fig 4A).

The fascia is elevated from the anterior half of the sternomastoid until the internal jugular vein, running along the edge of the muscle, can be seen in transparency. The sternomastoid vessels (one, or more often two) are transected (Fig 4B).

On the posterior border of the sternomastoid muscle, Erb's point is identified. This is the landmark for the spinal accessory nerve, as it emerges from the sternomastoid within 2 to 2.5 cm above Erb's point.[10,13] The posterior leaf of the fascia overlying the sternomastoid is elevated by means of sharp dissection, which is replaced by a blunt one near the spinal accessory nerve (Fig 4C).

Anteriorly, the fascial incision uncovers the outer aspect of the submandibular gland which is dissected from the fascia and, after ligature of the anterior facial vein, can be retracted superiorly in order to expose the stylohyoid and the posterior belly of the digastric muscle. These are completely freed from the fascia (Fig 4D).

DISSECTION OF THE LATERAL SPACE

Dissection of the Submuscular Recess. The surgical limits are, anteriorly, the internal jugular vein and the carotid artery, embedded in the carotid sheath; cephalad, the cranial base; posteriorly, the sternomastoid muscle anterior margin; and, on the floor of the recess, the levator muscle of the scapula dorsal margin.

Two retractors open the acute angle between digastric and sternomastoid muscles up to more than 90°. The transverse process of the atlas is palpated; this is the landmark to the internal jugular vein which is uncovered by blunt dissection together with the spinal accessory nerve which has usually already crossed the vein. The exposure of the vein is continued downward for 2 to 3 cm, interrupting, if necessary, the occipital vessels which cross it superficially (Fig 4E). The spinal accessory nerve is isolated until it enters the sternomastoid and is raised by means of a hook.

The dissection of the recess begins in its most cranial part by elevating the fascia from the floor, ie, from the longissimus and splenius muscles of the head. Below the transverse process, the dorsal margin of the levator muscle of the scapula must be identified, as it corresponds to the posterior limit of the dissection (Fig 4F).

Care must be taken along both the jugular vein and the sternomastoid. One must recall that at this level the jugular vein does not only lie over the carotid artery, but över and behind it; during dissection the vein must therefore be gently retracted ventrally so that the carotid wall can be reached. Along the sternomastoid, the deep angle formed between the muscle's outer and inner ends (from the sternum and clavicle, respectively) may contain a lymph node and must be accurately dissected. This step ends when the dissection of the recess has reached the point where the spinal accessory nerve enters the sternomastoid muscle.

Preparation of the Posterior Triangle. The spinal accessory nerve is isolated throughout its course, from its departure from the sternomastoid up to its entrance into the trapezius. When the latter has been identified, the outer fascia is elevated from its edge (Fig 4G).

Dissection of the Posterior Triangle. The surgical limits are, anteriorly the carotid sheath; posteriorly, the margin of the trapezius muscle; caudad, the upper clavicle border.

Dissection commences from the upper tip of the triangle by elevating the fascia which overlies the splenius muscle. As soon as the levator muscle of the scapula is reached, the specimen is connected with the one from the submuscular recess; the posterior edge of the sternomastoid is grasped and raised, and both fasciae, which cover the inner aspect of the sternomastoid and the surface of the levator muscle of the scapula, are elevated. (Attention must be paid to the proximity of the spinal accessory nerve which has a variable course in relation to the sternomastoid.) The block of the submuscular recess can now be extracted outside (Fig 4H).

As the dissection reaches the spinal accessory nerve, it is gently raised and the specimen is slid under it (Fig 4I). The subspinal part of the posterior triangle is dissected in a forward direction. From the border of the trapezius the floor of the space is exposed; some posterior branches of the cervical plexus, running superficially to the fascia, and the superficial and transverse cervical vessels are interrupted. When the omohyoid muscle is encountered it is completely freed from its fascia envelope and retracted. The posterior scalenic niche, between the anterior and middle scalene muscles, must be identified and handled carefully, as it contains the brachial plexus. Along the arbitrary boundary of the clavicle, the supraclavicular nerves are severed and the external jugular vein is ligated once more, as well as its branches.

Fig 4. A) Surgical field after elevation of skin and platysma muscle. Two ligatures are placed on external jugular vein, upper at inferior pole of parotid, lower in fossa ovalis where vein pierces fascia. Broken lines show incisions to be carried out in fascia. Arrow indicates Erb's point. B) Elevation of fascia from anterior half of sternomastoid muscle. Sternomastoid vessels (arrows) have been interrupted. C) Elevation of fascia from posterior half of sternomastoid muscle. Spinal nerve (arrow) is identified as it emerges from posterior border of muscle. D) Lower half of submandibular gland has been dissected from fascia and anterior facial vein has been ligated (arrow). Now posterior belly of digastric and stylohyoid muscles are exposed. E) Two retractors open widely angle between sternomastoid and digastric muscles. Transverse process of atlas, identified by palpation, is landmark for internal jugular vein (arrow), which is exposed together with spinal accessory nerve along its posterior edge and occipital vessels which cross ventrally to dorsally. F) Spinal accessory nerve is isolated until it penetrates into sternomastoid muscle and is raised. Below transverse process of atlas in floor of submuscular recess is levator muscle of scapula (*). Medially to it is internal jugular vein.

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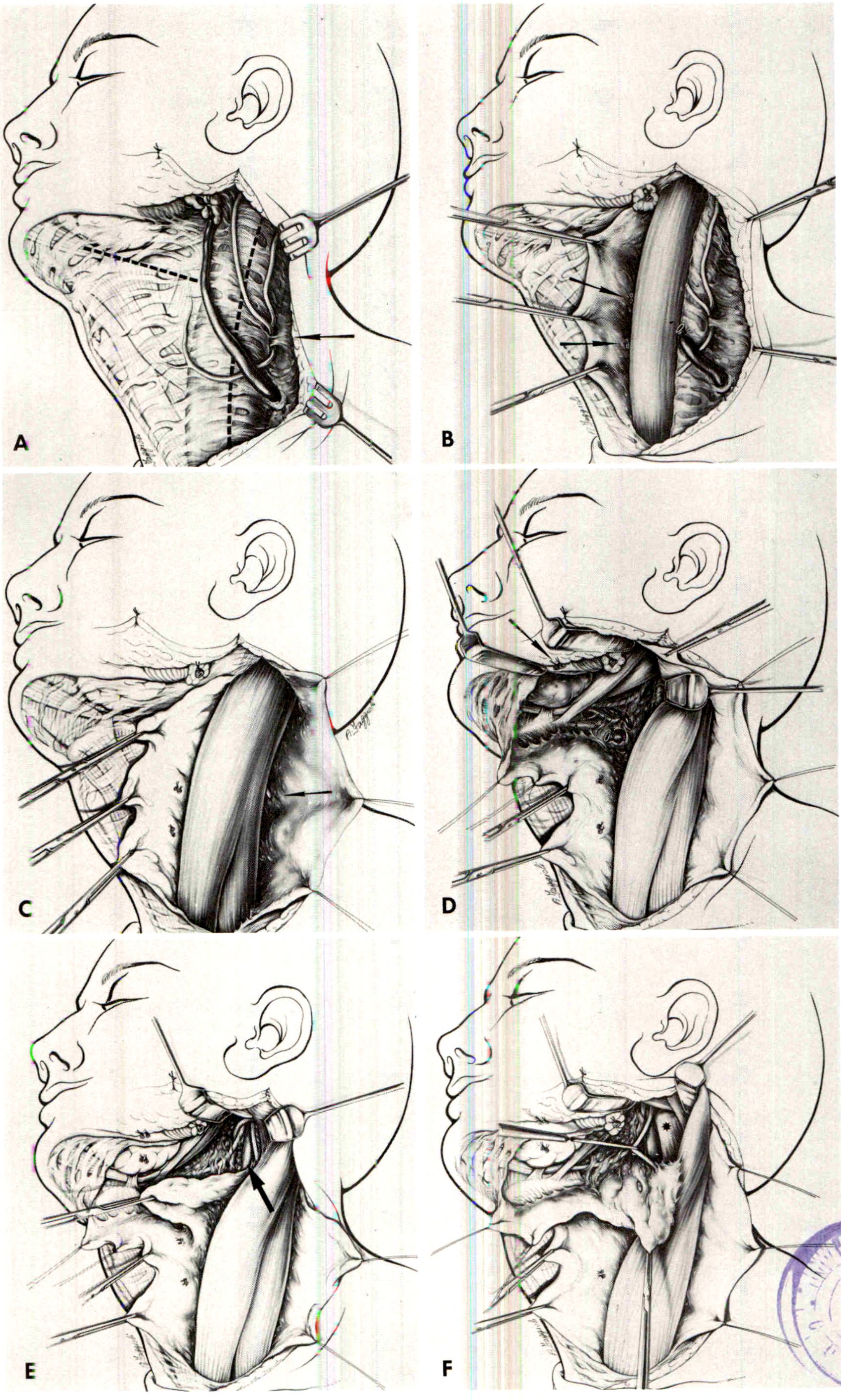
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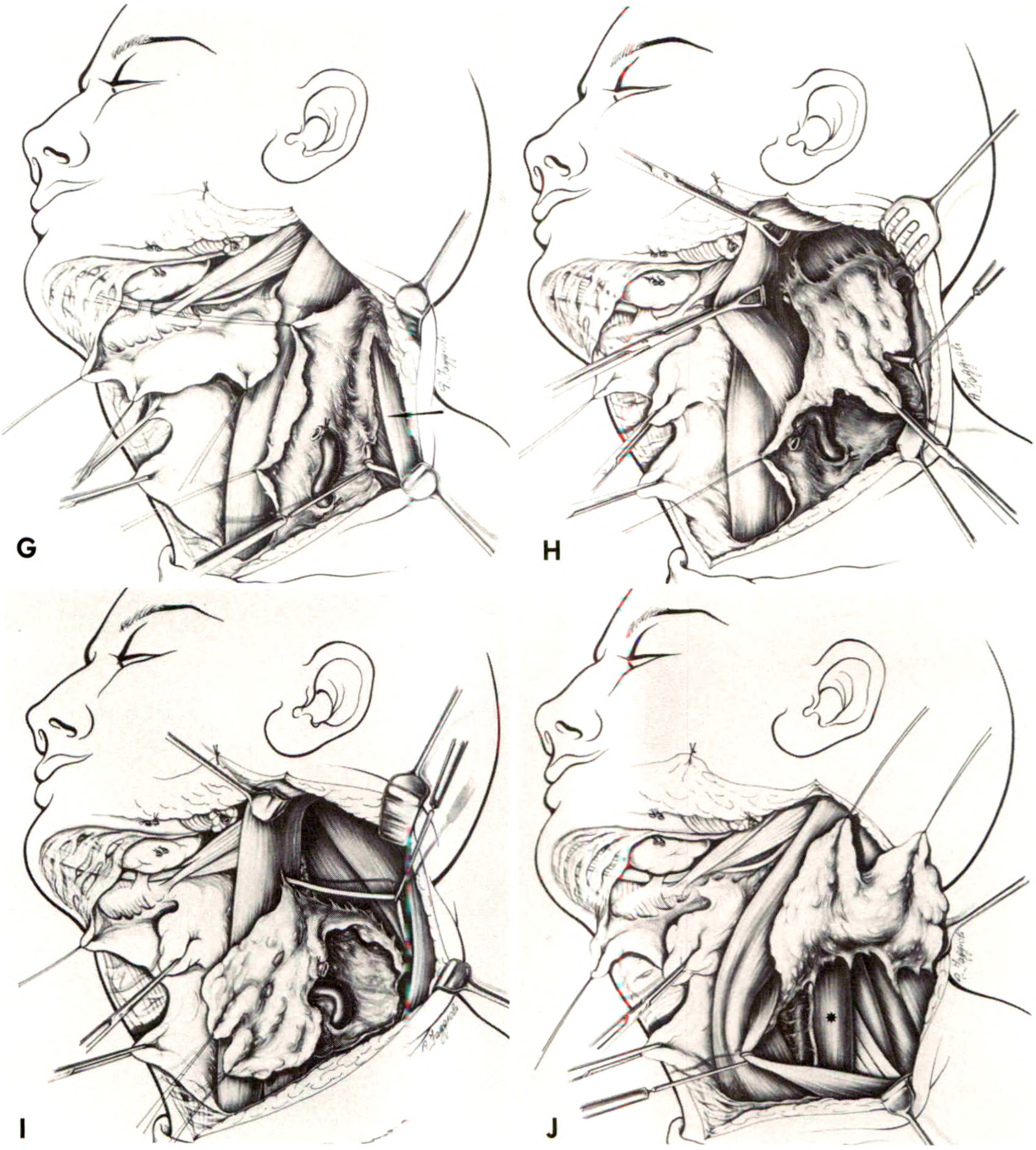

Fig 4, cont'd. G) Spinal accessory nerve (raised by hook) is skeletonized in posterior neck triangle. Fascia is then elevated from anterior border of trapezius muscle (arrow). H) Posterior border of sternomastoid is grasped and raised; fascia is elevated from deep aspect of this muscle and from surface of levator muscle of scapula; now specimen from submuscular recess can be slid underneath sternomastoid and extracted in posterior triangle. I) Spinal accessory nerve in posterior triangle is raised by means of hook and surgical block is slid under it. J) Dissection of lowest (subspinal) part of posterior triangle. Omohyoid muscle is freed from its fascia envelope and retracted. Brachial plexus in posterior scalenic niche between anterior (*) and middle scalene, phrenic nerve running along medial edge of anterior scalene muscle and, more medially, internal jugular vein are identified.

Elevation of the fascia on the anterior scalene muscle, must be accomplished after identification of the phrenic nerve which is often accompanied by a thin accessory branch. Then the posterior border of the sternomastoid near its clavicular attachment is retracted ventrally and the internal jugular vein and the carotid artery are exposed (Fig 4J). The thyrocervical trunk is ligated and, on the left side, the thoracic duct can be identified.

At this point the elevation of the fascia from the inner aspect of the sternomastoid can be completed everywhere. Two gauze loops are placed round the muscle which is drawn posteriorly, while the block, sliding under the muscle, is moved ventrally.

DISSECTION OF THE CAROTID SHEATH

The dissection is accomplished only in the length which corresponds to the paravisceral space, that is, from the upper edge of the thyroid gland to the intermediate tendon of the digastric muscle. The specimen is pulled ventrally and the posterior branches of the cervical plexus are severed, taking care to interrupt C-4 and C-3 distally to their connections with the phrenic nerve (Fig 4K).

A careful sharp dissection exposes the sympathetic trunk, the carotid adventitia with the vagus nerve (Fig 4L), and finally completely skeletonizes the internal jugular vein whose tributary branches are ligated (Fig 4M).

DISSECTION OF THE PARAVISCERAL SPACE

The surgical limits are laterally, the residue of the dissected carotid sheath; medially, the inferior constrictor, covered by the visceral sheath; cephalad, the posterior belly of the digastric muscle.

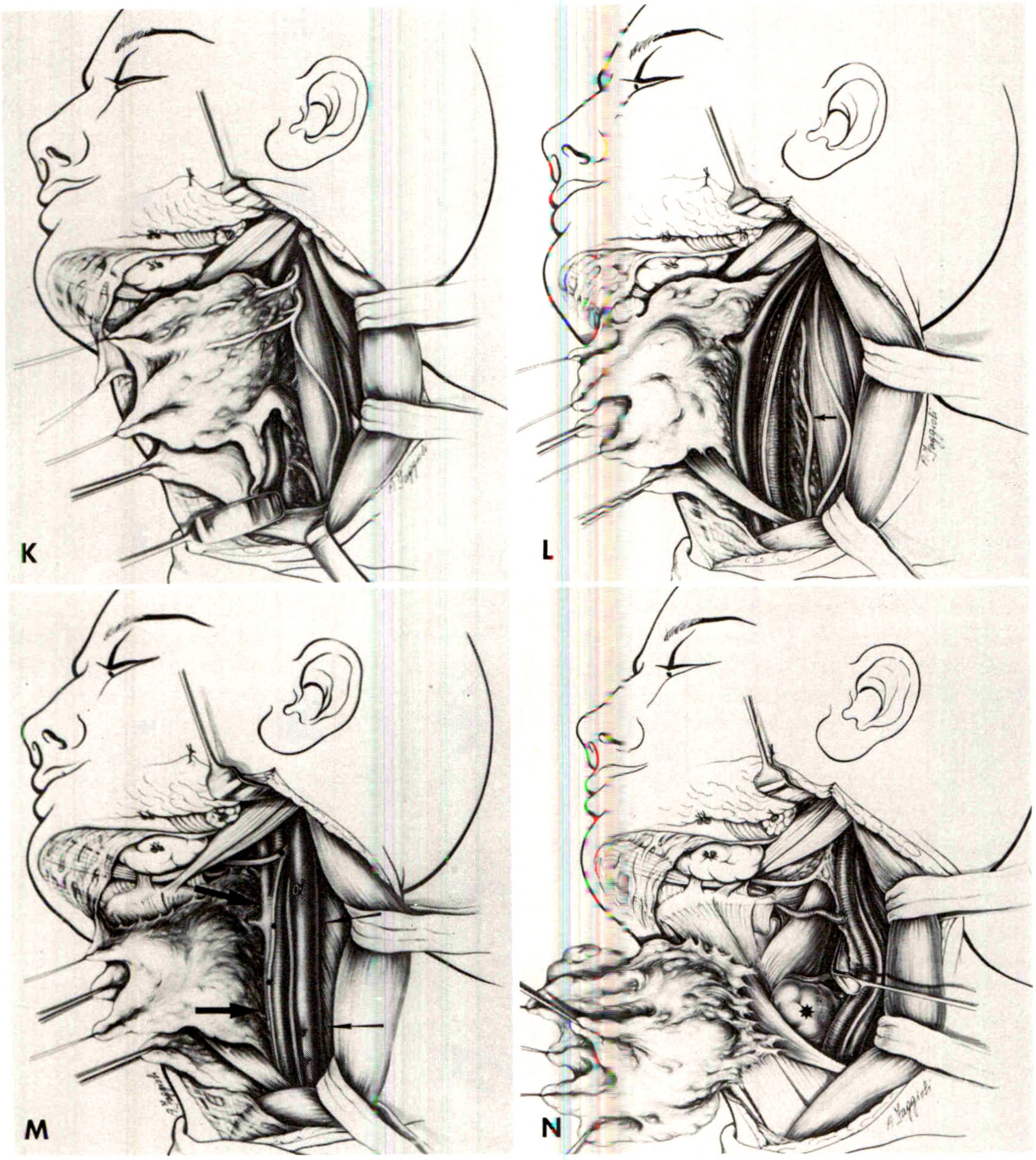

Fig 4, cont'd. K) Sternomastoid muscle, which has been completely uncovered from fascia, is retracted backward by means of gauze loops. Specimen has been slid under muscle and retracted toward median line. Dissection of carotid sheath begins with interrupting dorsal branches of cervical plexus (arrows) distally to their connections with phrenic nerve. L) Dissection of carotid sheath continues by uncovering sympathetic trunk (arrow), carotid artery and vagus nerve. M) Internal jugular vein (thin arrows on right) has been wholly skeletonized and its branches have been ligated. Vein now "falls" behind carotid artery (thick arrows on left) which is covered by hypoglossal nerve and descending ansa cervicalis (*). Between artery and vein is vagus nerve. N) Dissection of paravisceral space starts from superior pole of thyroid gland (*). Space is dissected, preserving anterior branches of carotid artery and skeletonizing hypoglossal nerve. Last step of FND ends when upper limit of space is reached, at level of posterior belly of digastric muscle.

The floor of this space is the sagittal aponeurosis, which includes the anterior branches of the carotid artery; these must not be injured. The dissection is directed cephalad and requires that the hypoglossal nerve be isolated from the surrounding venous plexus (Fig 4N).

Finally, the specimen adheres to the strap muscles; hence it can be removed in continuity with either a contralateral block or a submandibular dissection.

CLINICAL OBSERVATIONS

The first operation according to present technique was performed in July 1972. In July 1978 the total number of FNDs was 476, involving 265 patients, of whom 211 were treated bilaterally (only in 13 cases in separate sessions) and 54 unilaterally. The site of primary tumor is summarized in Table 1. The clinical stage of lymph nodes, according to the Union Internationale Contre le Cancer (UICC) classification (1978), is shown in Table 2.

Histologically positive nodes were found in 27 specimens which had been classified as N0, or N1A, or N2A, with 14.59% false negatives. Among the N1B-2B cases no malignancy was histologically

TABLE 1. SITE OF PRIMARY TUMOR

Site	No. of Patients
Larynx	195
Oral cavity	28
Pharynx (including tonsils)	12
Thyroid gland	10
Inferior lip	9
Other localizations (salivary glands, external and middle ear, skin of the head, etc)	11
Total	265

found in 43 specimens, with 53.75% false positives.

Seven patients died within the 30th postoperative day, but only in two did the cause of death appear to be directly related to the neck dissection; the first died on the 20th day from gangrene of the cervical tissues which caused sudden rupture of the internal jugular vein and the second died on the third day of a pulmonary embolism due to jugular thrombosis.

The most serious postoperative complication was the spontaneous rupture of the internal jugular vein in three cases. In the previously mentioned patient it was the consequence of a diffuse gangrene, but in two others it took place unexpectedly after few days and required an emergency ligature. To explain these occurrences one may suggest that during dissection the wall of the vessel had been inadvertently damaged; a subsequent increase in venous pressure gave rise to the hemorrhage. There is also the alternative possibility that a ligature placed on a tributary branch of the vein had loosened.

TABLE 2. CLINICAL STAGE OF LYMPH NODES

	Classification	No. of Patients
Clinically negative nodes	N_0	154
	N_{1A}	28
	N_{2A}	3
Clinically positive nodes	N_{1B}	63
	N_{2B}	17
Total		265

TABLE 3. RELATIONSHIP BETWEEN LYMPH NODE STAGE AND LOCAL RECURRENCES*

Classification	Histology	No. of Patients	Neck Recurrences
$N_{0\text{-}1A\text{-}2A}$	Negative	154	5 (3.25%)
	Positive	27	0
$N_{1B\text{-}2B}$	Negative	41	2 (4.88%)
	Positive	36	2 (5.55%)
Total†		258	9 (3.49%)

*Minimum follow-up three years.

Total excludes seven patients who died postoperatively.

Other postoperative complications were wound breakdown (13 cases) and serum or lymph collections (65 cases). To obviate this frequent mishap, we now routinely anchor the posterior triangle skin flap to the muscle layer by means of two or three stitches.

The list of iatrogenic complications includes the following: injury to the internal jugular vein, four cases (when the injury occurred during the first neck dissection in patients for whom a bilateral operation had been planned, the second dissection was deferred for 30 to 40 days); section of the thoracic duct, seven cases; section of the spinal accessory nerve, 12 cases; section of the phrenic nerve, five cases; section of the sympathetic trunk, four cases; section of the hypoglossal nerve, two cases.

The great majority of histologically positive patients received postoperative irradiation. Preoperative treatment, with doses ranging from 30 to 50 Gy, was administered only to 11 patients, in whom two wound breakdowns were observed.

To date (minimum follow-up three years), local recurrences were seen in nine patients (3.49%). The greatest delay between operation and discovery of the recurrence was 15 months. The relationship between recurrences and lymph node stage is summarized in Table 3.

REFERENCES

1. Crile G. Excision of cancer of the head and neck. JAMA 1906; 47:1780-6.

2. Bocca E. Supraglottic laryngectomy and functional neck dissection. J Laryngol Otol 1966; 80:831-8.

3. Bocca E. Critical analysis of the techniques and value of neck dissection. Nuovo Arch Ital Otol Rhinol Laringol 1976; 4:151-8.

4. Staffieri A. Lo svuotamento funzionale laterocervicale. III — Resoconto statistico. Nuovo Arch Ital Otol Rhinol Laringol 1976; 4:203-10.

5. Lingeman RE, Helmus C, Stephens R, Ulm J. Neck dissection: radical or conservative. Ann Otol Rhinol Laryngol 1977; 86:737-44.

6. Molinari R, Cantù G, Chiesa F, Grandi C. Retrospective comparison of conservative and radical neck dissection in laryngeal cancer. Ann Otol Rhinol Laryngol 1980; 89:578-81.

7. Bocca E, Pignataro O, Sasaki CT. Functional neck dissection. A description of operative technique. Arch Otolaryngol 1980; 106:524-7.

8. Bocca E, Pignataro O. A conservation technique in radical neck dissection. Ann Otol Rhinol Laryngol 1967; 76:975-88.

9. Suarez O. El problema de las metastasis linfaticas y alejadas del cancer de laringe e hipofaringe. Rev Otorrinolaringol Santiago 1963; 23:83-99.

10. Teatini GP, Zampano G.Lo svuotamento funzionale laterocervicale. I — Basi anatomiche. Nuovo Arch Ital Otol Rinol Laringol 1976; 4:159-76.

11. Pernkopf E. Topographische Anatomie des Menschen. München: Urban & Schwarzenberg, 1956.

12. Calearo CV, Teatini GP. Lo svuotamento funzionale laterocervicale. II — Tecnica chirurgica. Nuovo Arch Ital Otol Rinol Laringol 1976; 4:177-202.

13. Becker GO, Parell GJ. Technique of preserving the spinal accessory nerve during radical neck dissection. Laryngoscope 1979; 89:827-31.

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PERCEPTION OF SOUND THROUGH DIRECT OSCILLATION OF THE STAPES USING A PIEZOELECTRIC CERAMIC BIMORPH

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An ossicular vibrator of original design made from a piezoelectric ceramic bimorph was described. To test its effectiveness, the vibrator was temporarily implanted during tympanoplasty in four selected patients who had suffered extensive damage to the middle ear. By use of a special applicator, the vibrator was connected to either the stapes or the columella and was then excited by pure tone and speech signals. The subjects could hear well with the vibrator and distinguish speech signals. Thus a vibration threshold curve and a vibratory speech discrimination score were obtained. Comparing these with the results of conventional audiometry, the vibrator proved to be a highly efficient sound-conducting device. This study furthermore calls attention to some practical applications of this device, particularly to the possibility of implanting the vibrator as part of an implantable hearing aid.

INTRODUCTION

Despite technical refinement in reconstructive surgery performed in the sound-conductive mechanism of the middle ear, restoration of hearing to a socially adequate level has not always been achievable. In not less than 10% of patients with chronic otitis media, intractable pathologic changes have already taken place in the middle ear. Absence of stapedial superstructure, limited motility of the stapes, fibrosis of the tympanic cavity, extensive tympanosclerosis and obstruction of the eustachian tube are all grounds for a poor prognosis on postoperative hearing ability. Cochlear dysfunction associated with chronic middle ear inflammation also limits the prospects for improving hearing by surgery. Furthermore, in many congenital external and middle ear malformations, the procedures for reconstructive surgery of the sound-conducting mechanisms are not yet wholly dependable.

In such difficult cases, direct stimulation of the stapes using an artificial sound transducer has come to be considered a practical method of restoring socially adequate hearing ability. To this end, an ossicular vibrator of piezoelectric ceramic bimorph has been developed as a component of an implantable hearing aid. In the present study, this vibrator, attached to the auditory ossicles during a tympanoplasty operation, was found to be a promising device for converting electrical impulses directly into vibrations of the stapes, thereby compensating for a surgically irreparable deficiency of the sound-conducting mechanism of the middle ear. This paper explains the properties of this ceramic vibrator, describes how it functions in the middle ear, and presents the results of new research on sound perception induced by direct oscillation of the stapes utilizing the vibrator.

THE VIBRATOR

Piezoelectric crystals produce an electrical voltage in proportion to the distortion exerted on them by external forces. This phenomenon is termed the piezoelectric effect. Conversely, as shown in the upper half of Figure 1, crystals exhibiting the piezoelectric effect respond by vibrating when they are charged with alternating current. Lead titanate zirconate (Pb [Zr Ti] 0_3) is one of the most efficient piezoelectric materials available at the present time; it is commonly used in a ceramic form. This ceramic material is physically durable and preserves normal functions within a wide range of temperatures and changes in humidity.

The lower half of Figure 1 shows a bimorph adaptation of the piezoelectric ceramic element in which two ceramic elements with reversed polarity are pasted together. The free end of the piezoelectric ceramic bimorph will vibrate up and down in response to changes in the electric voltage applied to it while the other end remains fixed. Accordingly, an auditory ossicle coupled to the free end of the bimorph element will be stimulated by sound signals derived from the electrical impulses passing through the ceramic element.

The piezoelectric ceramic bimorph used in the present study was constructed in the form of a flat chip 7 mm in length, 1.2 mm in width, and 0.6 mm

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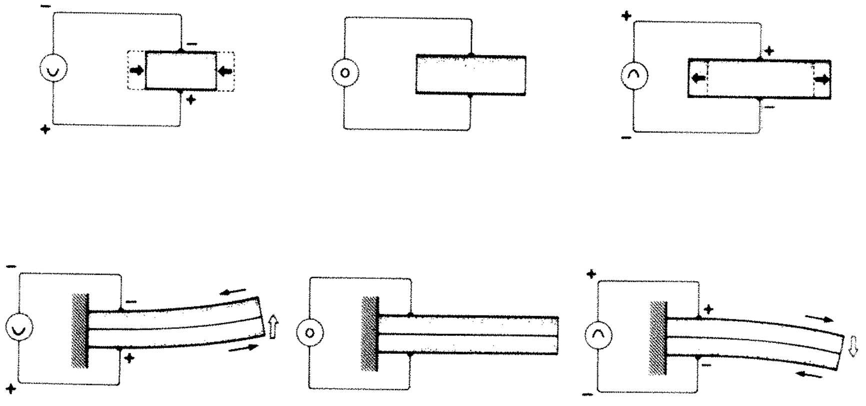

Fig 1. Functional principle of ossicular vibrator. Upper: Crystal with piezoelectric effect responds by vibrating when charged with alternating current. Lower: Free end of ceramic bimorph vibrates up and down in response to changes in electric voltage.

in thickness. The chip was coated to a thickness of 0.1 mm with fluorocarbon resin to provide insulation and biocompatibility. The electrical voltage was supplied by two silver-stranded wires insulated by the fluorocarbon resin. In order to secure good contact with the ossicle, a tip made of silicon rubber tubing was attached to the free end of the ceramic element.

The electrical impedance of the vibrator is capacitative, and the capacitance is about 1,400 pF. The output sensitivity reaches 0.4 µm/1V p-p at 1 kHz. Using a capacitative probe, frequency response at the tip was measured before and after implantation. Before the vibrator was attached to the stapes, the frequency response curve showed a sharp peak between 3 and 4 kHz. In order to measure the response curve after attachment, the device was implanted in the ears of several cats. When the tip was placed in contact with either the head or the footplate of the stapes, the frequency response curve smoothed up to 10 kHz due to the load of the perilymph. In fact, the vibratory motion of the stapes registered by the capacitative probe appeared to be a very close reproduction of the electrical waves imparted. Monitoring the cats' auditory brainstem responses to the vibrations of the stapes demonstrated that the vibrators still continued to function in the animals' middle ears after more than a year.

As part of the present study, multidimensional research on the vibrator has been carried out to determine efficacy, availability, and adaptability, in preparation for using it in the human ear. This paper reports the result of that part of the research which answers the following two questions: 1) Can the human subject hear sound without harmful consequences when the stapes is excited by the vibrator? 2) Can the human subject distinguish speech sound with the vibrator?

METHODS

Subjects. Four volunteer subjects with chronic otitis media were selected for this study. Preoperatively, conventional air and bone conduction audiograms were obtained and speech audiometry was carried out. All the patients understood the purpose of the experiment and what would be heard during the operation.

Operation. The operation was carried out under local anesthesia using 1% lidocaine with light preoperative sedation. The patients were conscious and alert during the test and their responses were reliable. Intact canal wall tympanoplasty was done in one patient and tympanoplasty with conservative radical mastoidectomy in the remaining three patients.

Application of Vibrator. The experiment employed an apparatus, shown in Figure 2, which had been designed to hold the vibrator in the appropriate position. After the proper position was determined, the base and the flange of the supporting column were temporarily glued using cyanoacrylate. Then the tip of the vibrator was attached very carefully and exactly to the head of the stapes. Where the superstructures were missing, the vibrator tip was attached to the top of a columella standing on the footplate.

Excitation of Vibrator. As shown in Figure 3, the lead wire of the vibrator was connected to the output terminal of the audiometer, their electrical impedances were matched, and pure tone signals from 0.25 to 8 kHz were fed into the vibrator at appropriate levels of intensity. Once the patient perceived sound, output intensity was attenuated step by step until he could hear nothing. In this way, the lowest audible intensity level on a decibel scale — the threshold — was determined. The read decibel value of the attenuator was converted into decibel re 1 V peak-to-peak using a conversion table. For convenience this threshold is termed the "vibration threshold" and the curve plotted for the thresholds of the various frequencies tested, the "vibration threshold curve."

Speech signals consisting of monosyllables selected from the Japanese syllabary and a list of one-figure numbers in Japanese

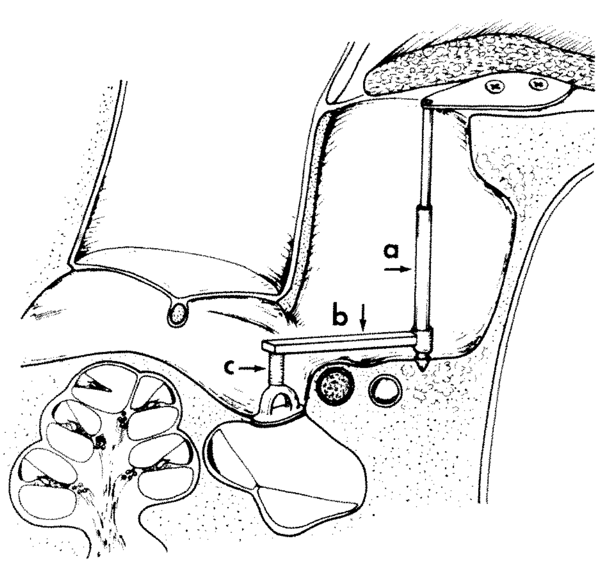

Fig 2. Implantation of vibrator in middle ear showing appliance (a) used to stabilize vibrator (b) which, in turn, is connected to stapes by columella (c).

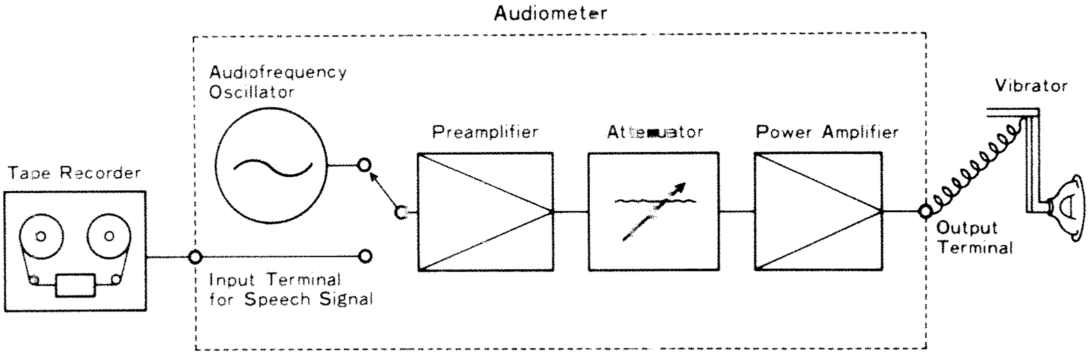

Fig 3. Method of excitation of ossicular vibrator.

were fed from a tape recorder (Sony TC3000SD) into the input terminal of the audiometer (AA34 Rion). The zero decibel of recorded sound was adjusted to the vibration threshold of 1 kHz. The patient's success on discriminating various sounds at each 10-dB increment was then calculated. The patient's score on this discrimination test is termed the "vibratory speech discrimination score."

RESULTS

In one subject, a 29-year-old man with tympanomastoid cholesteatoma, surgical treatment involved a two-staged operation, and the vibration threshold was accordingly measured twice, once during the first-stage and again during the second-stage operation. Figures 4 A,B and 5A compare the preoperative audiograms and the vibration threshold curves. In the case either of air conduction or of vibration sound, the patient could not hear sounds of 8 kHz. During the first-stage operation, all the ossicles except for the footplate of the stapes were found to be missing. The tip of the vibrator was therefore connected to the remnant of the posterior crus buried in the granulation tissue. The vibration threshold curve showed motility of the footplate was preserved from 0.25 to 1 kHz but sharply reduced beyond 1 kHz. Surgery then proceeded, a Silastic sheet was placed, and myringoplasty was performed. After nine months the completely healed and aerated middle ear was reopened. The vibration threshold curve now indicated excellent improvement on the motility of the footplate. On the other hand, the audiogram (Fig 4B), which was taken before the second-stage operation, revealed that the air-bone gap expanded further, a result which may be attributed to restoration of aeration in the tympanic cavity and to improved motility of both inner ear windows.

Figure 4C compares the speech discrimination scores obtained with conventional air conduction speech audiometry and those achieved with vibratory speech signals. With air conduction, a discrimination score of 100% was obtainable at 30 dB above the threshold of 1 kHz for both the monosyllabic and the number lists. With vibratory speech signals, on the other hand, the score reached 100% at 40 dB for the monosyllabic list and at 20 dB for the number list, figures which were compatible or even superior to the results of air conduction speech audiometry.

The Table summarizes for all four patients the preoperative mean bone conduction and air conduction thresholds, the maximum speech discrimination score and the maximum scores in vibratory speech discrimination. In three patients with mixed conductive deafness, speech discrimination scores reached 100% with both conventional air conduction speech audiometry and the ceramic vibrator.

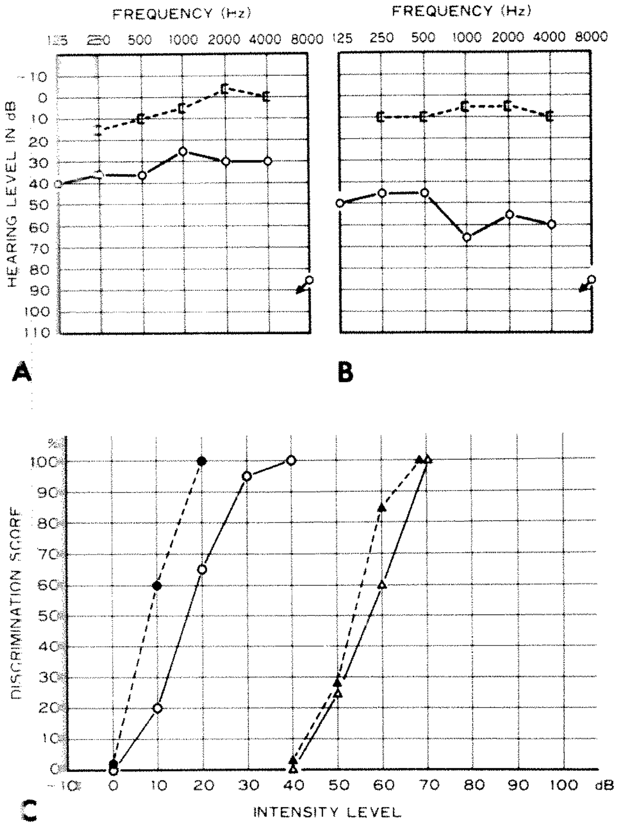

Fig 4. (Patient 1) Audiometric evaluation. A) Before first-stage operation; B) Before second-stage operation nine months later. C) Speech discrimination score assessed by conventional speech audiometries ▲-----▲ △——△ and by vibratory speech sounds ●-----● ○——○. ▲-----▲ ●-----● assessed utilizing list of single figure numbers and △——△ ○——○ assessed utilizing list of monosyllables.

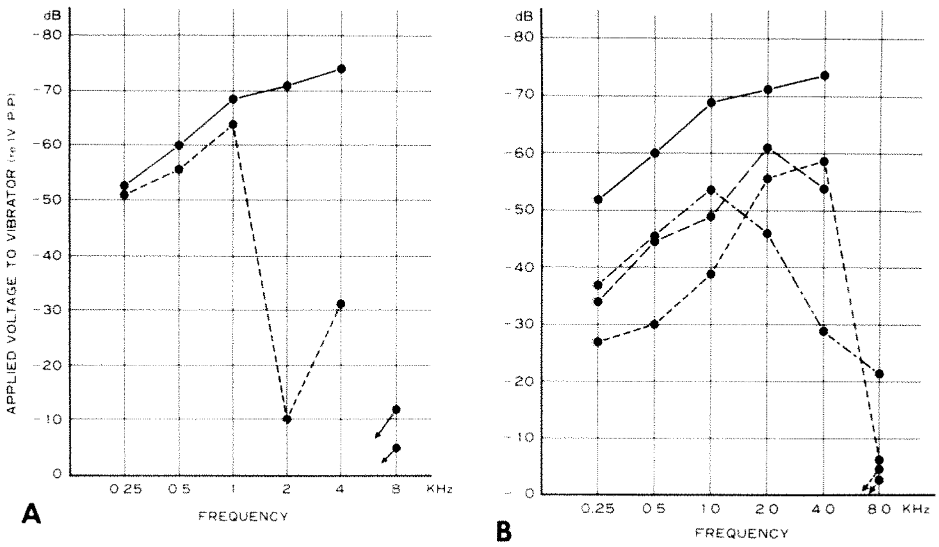

Fig 5. Vibration threshold curve. A) (Patient 1) ——— at first-stage operation; ——— at second-stage operation. B) (Four patients) Pt 1 ●——●; Pt 2 ●---●; Pt 3 ●···●; Pt 4 ●— — — —●.

In the case of the fourth patient, maximum discrimination with air conduction was 80%, whereas with the vibratory speech sounds, it extended to 90%. Considering that the discrimination scores for vibratory speech signals were obtained in an operating room, it can be assumed that speech sounds induced by the vibrator will be clearer and more intelligible in the soundproof room. The experimental evidence suggests that the quality of the sound induced by the vibrator is not at all inferior to that transmitted by the middle ear in its physiological state.

In Figure 5B, the vibration threshold curves of all the patients are presented. The threshold curves showed a gradual slope with its peak at 2 or 4 kHz depending on the patient. Within the frequency range of normal speech, however, the threshold curve is acceptably flat, and a dynamic range of more than 50 dB could be obtained regardless of the pathology of the stapes.

DISCUSSION

Postoperative follow-up studies on the present patients have disclosed no change in bone conduction and no additional complaints attributable to the intraoperative test procedure. It seems reasonable to conclude that the human subject can hear sound without harmful effects by using a vibrator of this type to activate the stapes. The speech sounds provided by the vibration of the stapes are clearly intelligible. The maximum discrimination score for vibratory speech sounds can reach 100%, even when the score is below 100%, it can still be expected to exceed results obtained by conventional speech audiometry.

By registering cochlear microphonic potentials in guinea pigs, Vernon et al[1] found that a "Denniston probe" made of a piezoelectric crystal, when placed in contact with the umbo of the eardrum, produced a response in the ear which was very similar to that produced by sound. That experiment also recorded the cochlear microphonic potentials while speech discrimination test material was being presented acoustically both to the external ear and, at a comparable intensity level, to the vibrating probe attached to the umbo. The recorded potentials were reproduced for subjects with normal hearing who then judged how intelligible the reproduced sounds were; in this way, a speech discrimination was obtained. The average speech discrimination was 60% with acoustically presented speech signals, whereas it was 76% with speech signals transmitted through the vibrating probe. The results of the present study on human subjects agree with the results obtained by Vernon et al[1] on guinea pigs. In view of all these findings, it seems reasonable to conclude that the speech signals transmitted by a ceramic vibrator are

COMPARISON OF RESULTS OF CONVENTIONAL AUDIOMETRY WITH THOSE OBTAINED BY VIBRATORY SOUND

Pt. No.	*Site of Excitation*	*Preop. Bone Conduction (dB)*	*Preop. Air Conduction (dB)*	*Vibration Threshold (dB)*	*Preop. Max Speech Discrim. Score (%)*	*Max. Discrim. Score of Vibratory Speech (%)*
1	Posterior crus of stapes	7.7	55.0	−66.7	100	100
2	Head of stapes	20.0	58.3	−41.7	100	100
3	Columella	26.7	53.3	−53.3	95	95
4	Columella	16.8	66.7	−48.3	80	90

more intelligible than those produced by a conventional air conduction earphone.

Previous experiments by the authors have already demonstrated that a vibrator of the type discussed here can keep functioning in the middle ear of a cat for more than a year. In another experiment, the vibrator was dipped in a saline solution at 40°C under five atmospheric pressures. Its sensitivity and frequency response remained stable under test conditions for more than 200 days. The consumption of electric power is incomparably smaller with the present vibrator than with other sound transducers such as a magnetic induction coil, which has been described by other researchers[2-4] as a potential component of an implantable hearing aid. Accumulated experience in performing, for example, a staged tympanoplasty employing Silastic sheeting, together with ossicular reconstructive surgery using carefully selected artificial materials, has confirmed that the middle ear can accept biocompatible artificial material, provided that inflammation has been brought well under control. Therefore, once account is taken of the results of the present study and of the above-mentioned advantageous properties of the vibrator, its implantation in conjunction with the second-stage operation must be considered a surgical technique likely to gain acceptance in the very near future.

Surgical procedure for the implantation of the vibrator will be described elsewhere. In this procedure, a transmitter in the form of a magnetic induction coil is implanted to excite the vibrator. The sound signals, processed by a microphone and an amplifier outside the ear, are supplied through the skin to the transmitter. Planning has been in progress on the utilization of the vibrator as an essential component of a totally implantable hearing aid.

Beyond these applications, the vibrator promises to be of use in several areas of otology. For example, the vibrator might be employed to estimate the ossicular chain functions, normal and pathologic, or be used as a device to pick up sound from the eardrum and ossicular chain. Further research will certainly expand the applications of the piezoelectric ceramic bimorph.

REFERENCES

1. Vernon J, Mahoney T, Schleuning A II. Implantable hearing aids. In: Northern JL, ed. Hearing disorders. Boston: Little, Brown and Company, 1976:249-68.
2. Goode RL. An implantable hearing aid, state of the art. Trans Am Acad Ophthalmol Otolaryngol 1970; 74:128-39.
3. Goode RL, Glattke TJ. Audition via electromagnetic induction. Arch Otolaryngol 1973; 98:23-6.
4. Fredrickson JM, Tomlinson DR, Davis ER, Odkvist LM. Evaluation of an electromagnetic implantable hearing aid. Can J Otolaryngol 1973; 2:53-62.

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AMERICAN BOARD OF OTOLARYNGOLOGY EXAMINATION

The American Board of Otolaryngology's written examination will be given September 25, 1983, at the Palmer House in Chicago, Illinois. Registration will be held Saturday, September 24, 1983, at 5:00 PM at the Palmer House. It is estimated that the examination will conclude at 6:00 PM Sunday.

Deadline for application is May 1. Please contact George F. Reed, MD, Secretary-Treasurer, at the American Board of Otolaryngology, 220 Collingwood, Suite 130, Ann Arbor, MI 48103, for new application forms.

Ann Otol Rhinol Laryngol 92:1983

ESOPHAGEAL DYSFUNCTION IN PATIENTS WITH CONTACT ULCER OF THE LARYNX

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Vocal abuse is the best-known etiological factor in contact ulcer. Other factors, such as hiatus hernia and gastroesophageal reflux have been discussed. A 12-year study of 58 male patients (mean age 52 years) with present or previous contact ulcers, is reported. Forty-three patients were investigated with esophageal function tests, ie, esophageal manometry including pH monitoring, acid-perfusion test, and acid-clearing test. Esophageal dysfunction was found in 74% which is significantly higher than the 30% found in the general population.

INTRODUCTION

Contact ulcer probably has a multifactorial etiology and the patient should be considered from several different aspects. Vocal abuse has been considered the most important etiological factor,[1-10] as also suggested by Jackson[1] who first described contact ulcer. He recommended a treatment consisting of vocal rest for long periods, and in some cases, vocal rest combined with surgical excision.[2] In 1947, Peacher and Holinger[3] reported good results using voice therapy, since confirmed by others.[4-10] Patients with contact ulcers have a low-pitch pressed quality of voice as their most pronounced feature. In addition, they often have laryngeal pain and irritation as well as a frequent need to cough and clear the throat. These nonlinguistic phenomena together with heavy lifting and straining make the vocal processes rub against each other.[6,8] Emotional stress is considered as another etiological factor.[6,7,9] Constitutional factors obviously play an important role as the patients are almost exclusively males.[6,11]

Ward and his colleagues[12] suggested hiatal hernia, found in 18 of 28 patients with contact ulcers, as another etiological factor. Ulcers and granulomas regressed following antireflux therapy. Esophageal reflux has also been discussed earlier[13-15] and, it is interesting to note, in 1928 Jackson[1] found that "many of the patients complained of waking with a choking, strangling cough at night, relieved after secretions were coughed out of the trachea." He suggested that this was due to oral secretions carrying infection. The same symptoms were described by Ward and colleagues who related the symptoms to esophageal reflux and aspiration of gastric content. However, voice therapy, in some instances combined with surgery, has been the treatment of choice in many centers. This treatment has to be considerably prolonged and the contact ulcers often show a high tendency to recur. The aim of this study was to see if patients with contact ulcers have a higher frequency of esophageal dysfunction (ED) than the general population.

MATERIAL AND METHODS

This study comprised 58 patients, all men, with a mean age of 52 years (range 29 to 78). They were treated for contact ulcers and granulomas from 1969 to 1980. Twenty-six patients stated a voice-straining job and/or were active singers. Five patients worked in noisy industrial environments. Twelve were smokers, 21 had stopped smoking several years before, and the remaining 25 had never smoked. An upper respiratory tract infection preceded the symptoms of contact ulcer in 19 patients, and six reported a new job or an increased workload. The contact ulcer was twice as common on the left side (33 patients) as on the right side (16 patients). Nine patients had bilateral lesions.

Most patients had received voice therapy, and the majority had a direct laryngoscopy performed. During the first 7 years only small biopsy specimens were removed, but during the last 3 years more often the entire lesion has been excised in an attempt to hasten the healing (Table 1). In all, 30 patients had voice therapy only and 21 had voice therapy combined with surgical excision. Seven patients did not receive voice therapy because the symptoms were only minor. One of these, however, had his lesion excised. No one was treated for ED.

The patient records do not allow a retrospective determination of the cure-time. We have used the number of sessions of voice therapy for each patient as an indirect measure of healing. We found no difference between the patients treated with voice therapy alone and those treated with voice therapy and excision. Both groups had an average of about 25 sessions per patient. Most patients had completed therapy within 12 months but a few patients had considerably prolonged therapy.

Many patients were not able to work because of voice problems. The patients had a mean sick leave of 72 days (range 0 to 474 days). This information on 43 patients has been obtained from the social insurance service. The mean sick leave of the general 50- to 54-year-old male population in the same area was 20 days in 1980. The reexamination with mirror laryngoscopy of 46 patients showed that 11 (25%) had active ulcers. Five of these were still under treatment, and six were old cases whose ulcers had healed after initial treatment but later relapsed. The history of these ulcers varied from 1 month to 5 years.

In the 1981 follow-up all patients received a postal questionnaire.[16] Answers were obtained from 52 of 58 patients. Four patients had died, and two did not answer the letter. At the follow-up, mirror laryngoscopy was performed in 46 patients, and of these 43 were tested with esophageal manometry, the acid-

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TABLE 1. NUMBER OF LARYNGOSCOPIES AND EXCISIONS OF CONTACT ULCERS OR GRANULOMAS AT TWO DIFFERENT TIME PERIODS

	Time Period	
	1969 to 1977	*1978 to 1986*
No. of patients	33	25
Laryngoscopies	20	15
Excisions	8	14

perfusion test, and the acid-clearing test. Five patients had moved to distant parts of the country and one did not come to the reexamination for other reasons. Another three patients declined to participate in the esophageal function tests. The different esophageal tests were performed according to the methodology described by Kjellén.[17] The patients were regarded as having ED if one or more of the following criteria were met: positive related acid perfusion test, pathological acid clearing test, dysmotility, indirect or direct signs of hiatal hernia, and gastroesophageal reflux at abdominal compression.

RESULTS

Of the 52 patients who answered the questionnaire, 15 (29%) had symptoms suggesting ED. Forty-three were investigated with esophageal function tests, 32 had ED (74%). The same frequency of dysfunction was found in the group of patients with active contact ulcers (8/11) as in those without. The different pathological findings are shown in Table 2.

DISCUSSION

Ward and colleagues[12] stressed the importance of hiatal hernia and gastroesophageal reflux as etiological mechanisms in contact ulcers of the larynx and reported good results with antireflux therapy. In the present study, 74% (32/43) of the tested patients had ED. If the remaining patients (15) are considered as negative there are still 55% (32/58) who had ED. About 30% of the general population, with an age corresponding to that of our patients, have ED.[18] In this connection it has to be noted that the esophageal examination was not performed in close relation to the diagnosis of the contact ulcer, which may influence the results. However, the ratio of ED in those patients with a contact ulcer present at the esophageal manometry was the same as in those without.

The question is whether ED is of etiological importance in contact ulcers or if there is a common denominator for ED and contact ulcer. Ward and colleagues[12] suggested that spillover of gastric contents into the pharynx at night caused a sudden awakening, coughing, and throat-clearing, traumatizing the vocal processes. Another possibility may be a direct inflammatory effect on the laryngeal mucosa of gastric juice.[15] Respiratory complications in gastroesophageal reflux have been described,[19] and patients with bronchial asthma have been reported to have an increased frequency of ED.[17] In the patients with bronchial asthma, a neurogenic esophagobronchial reflex mediated by the vagus nerve has also been suggested. When acid enters the lower part of the esophagus, bronchial obstruction occurs. A similar reflex mechanism might possibly operate in patients with contact ulcers; acid in the esophagus may give a cough reflex or cause a laryngeal dysfunction.

TABLE 2. RESULTS OF THE ESOPHAGEAL FUNCTION TESTS IN 43 PATIENTS WITH PREVIOUS OR PRESENT HISTORY OF CONTACT ULCER OR GRANULOMA

Esophageal Findings	*No. of Patients*
Normal findings	11
Esophageal dysfunction	32
Hiatal hernia	13
Gastroesophageal reflux	22
Dysmotility	10
Pathological acid-clearing test	16
Insufficient upper sphincter	5
Insufficient lower sphincter	5
Pathological acid-perfusion test	3

Urschel and Paulson[20] studied 636 patients with hiatal hernia and gastroesophageal reflux. They found a high incidence of tracheobronchial and pulmonary complications with significant respiratory symptoms in 61%. In 16%, respiratory symptoms were the only sign of gastroesophageal reflux. In our study only 29% had symptoms of ED. Therefore it seems important to consider laryngeal symptoms as a possible sign of ED. This was not the case in the questionnaire used in our study.

In an American veterinary study[21] contact ulcers were found in 13.1% of 30,444 cattle larynges. On the basis of bacteriological examinations, an infectious etiology was suggested. In our study 32% of the patients reported an upper respiratory tract infection preceding the onset of the symptoms. This is probably one of several triggering factors for contact ulcers. Smoking, however, does not seem to be important for etiology or healing of contact ulcers. There was an even lower percentage of smokers in the present study than in the general Swedish population, where in 1976,[22] about 40% of the adults were smokers.

It was difficult to find a good way to compare the healing effect of voice therapy alone with that of voice therapy combined with surgery. There was no difference between the two groups of patients when counting the number of voice therapy sessions. However, the study was retrospective and covered a long period of time. Many factors may have influenced the number of therapy sessions. Theoretically, however, surgical excisions of at least large granulomas must be considered a prerequisite for successful voice therapy.[11] The effect of ED treatment on contact ulcer has not yet been evaluated but will be the scope of a future study.

CONCLUSIONS

Esophageal dysfunction may be of etiological importance in contact ulcer of the larynx since the frequency of ED was more than twice as high in patients with present or previous ulcers than in subjects of corresponding age in the general population.

REFERENCES

1. Jackson C. Contact ulcer of the larynx. Ann Otol Rhinol Laryngol 1928; 37:227-30.

2. Jackson C, Jackson CL. Contact ulcer of the larynx. Arch Otolaryngol 1935; 22:1-15.

3. Peacher G, Holinger P. Contact ulcer of the larynx: II. The role of vocal reeducation. Arch Otolaryngol 1947; 46:617-23.

4. Holinger PH, Johnston KC. Contact ulcer of the larynx. JAMA 1960; 172:511-5.

5. Von Leden H, Moore P. Contact ulcer of the larynx: experimental observations. Arch Otolaryngol 1960; 72:746-52.

6. Brodnitz FS. Contact ulcer of the larynx. Arch Otolaryngol 1961; 74:70-80.

7. Peacher GM. Vocal therapy for contact ulcer of the larynx. A follow-up of 70 patients. Laryngoscope 1961; 71:37-47.

8. Cooper M, Nahum AM. Vocal rehabilitation for contact ulcer of the larynx. Arch Otolaryngol 1967; 85:41-6.

9. Bloch CS, Gould WJ. Vocal therapy in lieu of surgery for contact granuloma: a case report. J Speech Hear Dis 1974; 39: 478-85.

10. Bloch CS, Gould WJ, Hirano M. Effect of voice therapy on contact granuloma of the vocal fold. Ann Otol Rhinol Laryngol 1981; 90:48-52.

11. Kleinsasser O. Mikrolaryngoskopie und endolaryngeale Mikrochirurgie. Technik und typische Befunde. Stuttgart, New York: FK Schattauer Verlag, 1976, 139-42.

12. Ward PH, Zwitman D, Hanson D, Berci G. Contact ulcers and granulomas of the larynx: new insights into their etiology as a basis for more rational treatment. Otolaryngol Head Neck Surg 1980; 88:262-9.

13. Cherry J, Margulies SI. Contact ulcer of the larynx. Laryngoscope 1968; 78:1937-40.

14. Delahunty JE, Cherry J. Experimentally produced vocal cord granulomas. Laryngoscope 1968; 78:1941-7.

15. Goldberg M, Noyek AM, Pritzler KPH. Laryngeal granuloma secondary to gastro-oesophageal reflux. J Otolaryngol 1978; 7:196-202.

16. Areskog M. Angina-like chest pain. A study with special reference to oesophageal dysfunction and ischaemic heart disease. [Medical Dissertation No. 90]. Linköping: Linköping University, 1980.

17. Kjellén G. Oesophageal dysfunction and bronchial asthma [Medical Dissertation No. 111]. Linköping: Linköping University, 1981.

18. Tibbling L. Oesophageal dysfunction and angina pectoris in a Swedish population selected at random. Acta Med Scand 1981; Suppl 644:71-4.

19. Belsey R. The pulmonary complications of oesophageal disease. Br J Dis Chest 1960; 54:342-8.

20. Urschel HC, Paulson DL. Gastroesophageal reflux and hiatal hernia. Complications and therapy. J Thorac Cardiovasc Surg 1967; 53:21-32.

21. Jensen R, Lauerman LH, Braddy PM, et al. Laryngeal contact ulcers in feedlot cattle. Vet Pathol 1980; 17:667-71.

22. Svenska folkets rökvanor 1976. Results from a study made by the Swedish Institute for Public Opinion Research on behalf of the Swedish Association of Nonsmokers and the insurance company Trygg Hansa.

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SIXTEENTH ANNUAL CONFERENCE OF THE INDIAN SPEECH AND HEARING ASSOCIATION

The 16th Annual Conference of the Indian Speech and Hearing Association (ISHA) will be held January 27-29, 1984, at Madras, India. Papers on all aspects of speech-hearing and language are invited for submission. Those interested in presenting papers should submit an abstract of not more than 200 words. English will be the official language of the conference. For further information contact J. Dayalan Samuel, Secretary, ISHA, All India Institute of Speech and Hearing, Manasagangothri, Mysore 570 006, India.

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EXPERIMENTAL STUDY OF VELOCITY FIELDS IN A HUMAN NASAL FOSSA BY LASER ANEMOMETRY

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Velocity fields were mapped in a model of a human nasal fossa by laser doppler velocimetry, an innovative, quantitative and noninvasive method of optical anemometry, and by computerization. Other pertinent parameters were also calculated. Studies made at different cross sections of the nasal fossa showed the very definite influence not only of shapes and dimensions but also of direction of flow on velocity fields. The turbinates had a streamlining effect on the velocity fields while the liminal valve had a directional effect. Flow was usually greater in the lower half of the fossa and closer to the septum. The flow was generally turbulent. Velocity fields appear to give more information on intranasal aerodynamics than the calculated flow and Reynolds number for the sections studied, and this allows one to at least theorize that there may be an aerodynamic basis to certain pathological conditions of the nasal airway and its adjoining cavities, the paranasal sinuses, and the eustachian tubes.

INTRODUCTION

Many years ago when rhinomanometry was used experimentally, it was felt by one of the present authors that, although it would eventually become a clinical tool to differentiate between variable and fixed nasal obstruction and to quantify the degree of each as well as the result of therapeutic measures,[1,2] it would not give information about flow characteristics within the nasal fossae. It also became evident that measurements of velocity fields within the nasal fossae required the skills of engineers as well as those of rhinologists. This paper is the result of many years of collaboration between the engineering school of the Ecole Polytechnique of Montreal and the Department of Surgery of the University of Montreal. It brings to clinical attention some of the results published in a thesis for postgraduate studies in mechanical engineering, where details of mathematical formulas and calculations can be found.[3]

This experimental study was carried out to obtain velocity fields in the model of one nasal fossa using optical anemometry. Although others[4-7] have studied airflow in the nose, this is believed to be the first publication of a noninvasive, quantitative, and dynamic study of flow characteristics in a nasal fossa. A velocity field is the tridimensional presentation of air velocity distribution through a cross section of a conduit. It is a dynamic data as opposed to static data obtained by pressure gradient.

Measurement of velocity field by a laser doppler velocimeter (LDV) required the use of a transparent model of the nasal fossa. Since no previous study had been done utilizing this technique, no points of reference were available and readings were made at cross sections that appeared to be of theoretical and clinical importance. Measurements were made only for continuous flows. The results are valid only for the aerodynamic effects of the shapes and dimensions of the nasal fossa. These results do not take into account the biological effects of elasticity, the variation in anatomy, the effect of the mucosa and the mucus covering of the human nose.

MATERIALS AND METHODS

Experimental Setup. A calibrated flow of air containing standardized water particles in suspension was pumped through the model preparation. Pinpoint air velocity was determined by measuring the speed of water particles with the LDV. The experimental setup (Fig 1) consisted of the model of one nasal fossa, an air pump, a particle generator, and an LDV. The LDV was mounted on a grid system in such a way that mapping of air velocity for any cross section of the model was possible.

Model. The model was prepared from the imprint of a normal human fossa and pharynx. Silicone (GE RTV-118) was injected with a large syringe and a catheter through the nostrils of a cadaver, filling the nasal fossae and upper pharynx. There appeared to be no deformity induced by the introduction of the silicone.

After adequate curing of the silicone, the anatomical material was dissected from the imprint which was then immersed into liquid bioplastic. After proper curing, a sagittal division of the bioplastic bloc was made at the area of the septum and the imprint was removed from the bioplastic model. Because of the optical characteristics of the laser anemometer, the septum of the model had to be replaced by a thin sheet of transparent acrylic which was sealed to the model. The model reproduced only that portion of the pharyngeal airway corresponding to the nasal fossa. Acrylic tubes were fitted to the vestibule and to the pharyngeal ends of the fossa to allow connection with the air-generating apparatus. The internal dimensions of the model were obtained using the LDV mounted on a grid system (Fig 2).

Laser Doppler Velocimeter. A 15mW ThermoSystems (TSI 900-2) laser (He-Ne) doppler velocimeter was used to measure air velocity in the model. In fact, the LDV measures the speed of very small particles introduced in suspension into the airflow. The laser beam is a coherent light source, and when a particle passes in front of it, a decrease in the intensity of the light takes place. If more than one particle passes in front of the light source, areas of

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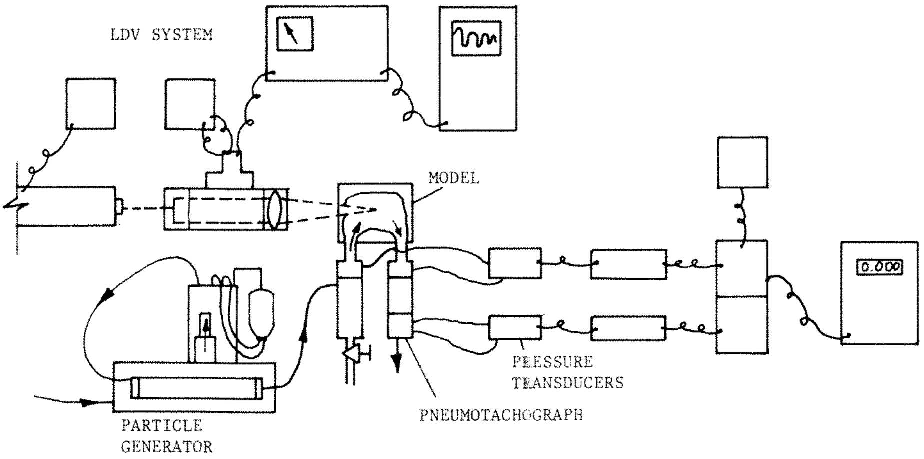


Fig 1. Experimental setup.

high- and low-light intensity are created. These areas are then interpreted by a photocell as variation in frequency linearly proportional to the speed of the particles when these particles are generated in homogeneous quantity; dimension and the velocity of the airflow at that point can be determined.

Particle Generator. A ThermoSystems TSI 3060 particle generator was used to produce the water particles utilized in this study. This generator produces aerosol droplets through the ultrafrequency vibrations of a crystal. The size and quantity of water particles introduced in the model were controlled by passage of the aerosol through a filtration chamber.

Airflow. A 3.29 L/s (10 L/min) Fleisch pneumotachograph and a Statham PM5TC pressure transducer of ± 28 mm water capacity were used to measure the flow of air through the model. Particle generator on and off readings indicated no detectable change in flow rate, therefore, it was assumed that the humidity introduced by the particles did not affect the calibration of the pneumotachograph. The pressure gradient of the model was measured with a Statham PM 15E pressure transducer of ± 106 mm water capacity.

A Statham SC 1100 conditioner was used to ensure proper voltage in the Wheastone bridge at low-flow condition. An electronic filter was used to eliminate the 60-Hz interference of the electronomometer exit voltage.

A continuous flow rate of 0.166 L/s was selected for this experimental study. This flow rate is a compromise between a mean flow rate through one nasal fossa taking into account the presence of the nasal cycle and the peak flow rate for normal breathing.

Nasal Fossa Cross Sections Studied. The five cross sections studied are shown in Figure 2. Section A is the liminal valve area. This is the area where the greatest resistance to airflow takes place. It has been called the "flow-limiting segment."[8] Sections B, C, and D are the preturbinal, turbinal and postturbinal areas, respectively. These areas present a great variation in cross section according to the height of the fossa. Excluding the variation in size of the turbinate due to the nasal cycle, it was obvious that a knowledge about the velocity field before, during, and after the turbinal area could help in understanding the aerodynamic role of the turbinates. Section E is the area of the nasopharynx. This area, immediately behind the nasal fossa, is important because the airflow changes direction in a small cross section. Sections C and E were studied for inspiration only and data is reported in the Table only.

Procedure of the Experimental Study. The laser source was mounted on a grid system allowing movement and positioning in three dimensions. Exact positioning of the laser beam was thus possible for the three coordinates of depth, width, and height in relationship to the immobile nasal model. This reproducible and precise "fix" of the laser beam was used to determine the velocity at all measurement points.

In Figure 3, depth represents a given cross section of the nasal fossa on an anteroposterior line from the vestibule to the nasopharynx. The width is found on ordinate OX and the height on ordinate OY. Note that the normal anatomical orientation has been reversed, the floor of the nose being "up" on the drawing and the roof being "down," because the tridimensional effect of the plotting of the measurements of velocity is best visualized this way. The third ordinate, OX, shows the velocity of a particle measured at one coordinate (as indicated by the arrows on the grid). The interrupted lines parallel to ordinate OX and joining the arrows are velocity profiles. They were obtained for each cross section by moving the laser beam along ordinates OX and OY, the measurements being made from the septum to the lateral wall and from the floor to the roof of the nose. The distance between the measurement points varied from 0.1 mm to 0.5 mm depending on the irregularity of the cross section. Between 100 and 350 measurement points were made for each section.

Measurements at each cross section were validated by integration planimetry and by numerical integration. The velocity profiles measured for each cross section were integrated by planimetry and by the simple formula $\dot{V} = fX$, where $\dot{V}$ = velocity, f = function of the distance X. The cross section measurements were considered valid when the integration values were within 10% of the present flow of 0.166 L/s through the model. These values were also spot-checked by the more complicated numerical integration method.

RESULTS AND ANALYSIS

Velocity fields for Sections A, B, and D during inspiration and expiration are shown in Figure 4. These velocity fields are tridimensional representations of the flow obtained by computer processing of all measurement points for each cross section. As

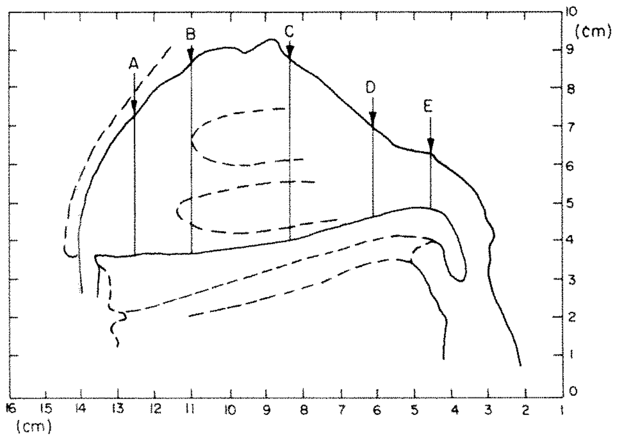


Fig 2. Outline of model with measured dimensions. Sections of measurements are A, B, C, D, and E.

CALCULATED DATA FOR SECTIONS A THROUGH E

Cross Section	*Y_T cm*	*X_T cm*	*A_T cm*	*$\dot{V}$ cm/s*	*Q_{nom} cm³/s*	*Q_T cm³/s*	*Diff %*	*Re*
Inspiration								
A	3.06	0.614	1.879	96	164	180	+ 9.8	1,320
B	4.71	0.635	2.991	66	177	198	+ 11.9	992
C	5.00	0.504	2.521	62	170	157	7.6	765
D	2.44	0.957	2.336	74	177	172	− 2.8	1,360
E	1.16	0.734	0.851	197	173	168	− 3.1	2,380
Expiration								
A	3.05	0.621	1.894	83	165	157	− 4.9	1,150
B	4.97	0.533	2.651	59	165	157	− 4.9	765
D	2.21	1.013	2.239	69	165	155	− 6.1	1,290

Y_T - Max height cm; X_T - Max width cm; A_T - Cross section cm²; $\dot{V}$ - Flow cm³/s; Q_{nom} Nominal flow introduced in the model cm³/s; Q_T - Calculated flow cm³/s; Diff - Difference between nominal and calculated flow percentage; Re - Reynolds number = $\frac{\dot{V}D_H}{\upsilon}$, ($\dot{V}$ = Velocity, D_H = Hydraulic diameter, υ = Viscosity of air 20°C - 0.149 cm²/s).

previously mentioned, the normal anatomical orientation has been reversed; the floor of the cavity is up and the roof is down on the printout. The printout is not an exact anatomical representation of the normal fossa. The constant velocity curve allows convenient localization of maximum velocity and flow. Flow is said to be more uniform or streamlined when the constant velocity curves are longer. Uniform flow indicates a more even distribution of air through the cavity with lower peak velocity.

The following values were also calculated for each cross section: the maximum height, Y_T, the average width, X_T, the cross section area, A_T, the hydraulic diameter, D_H, the average velocity, $\dot{V}$, and the Reynolds number, Re. These values are shown in the Table.

Section A is located immediately posterior to the liminal valve. It is the smallest and the most regularly shaped nasal cross section.

The velocity profile obtained during inspiration is reported in Figure 4A(1). It shows a flow in excess of 105 cm/s near the floor and lateral aspect of the section. This high velocity was believed to be due to the directional effect of the liminal valve. A low flow condition is present in the upper part of the cross section.

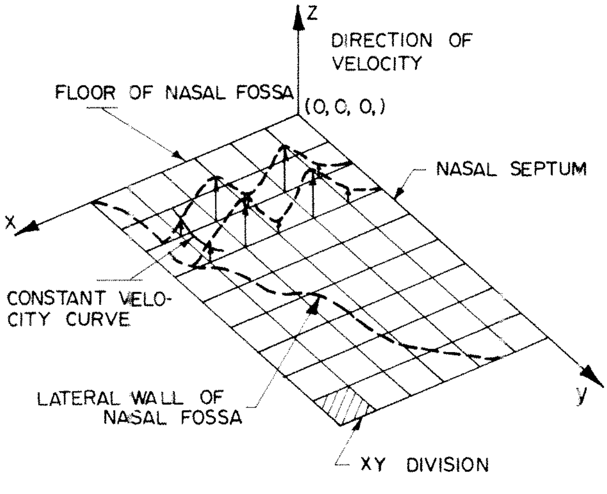


Fig 3. Three-dimensional coordinate system used in mapping velocity fields by computer.

The velocity profile obtained during expiration is reported in Figure 4A(2). The flow is more uniformly distributed through the whole section; it is only slightly more elevated in the lower portion. The velocity field has been considerably streamlined when compared to Section B, reported in Figure 4B(2). This streamlining effect takes place a short distance after passage through the turbinate area.

Section B is located at the beginning of the turbinate area during inspiration and at the end of it during expiration. It is the largest nasal cross section area and is irregularly shaped.

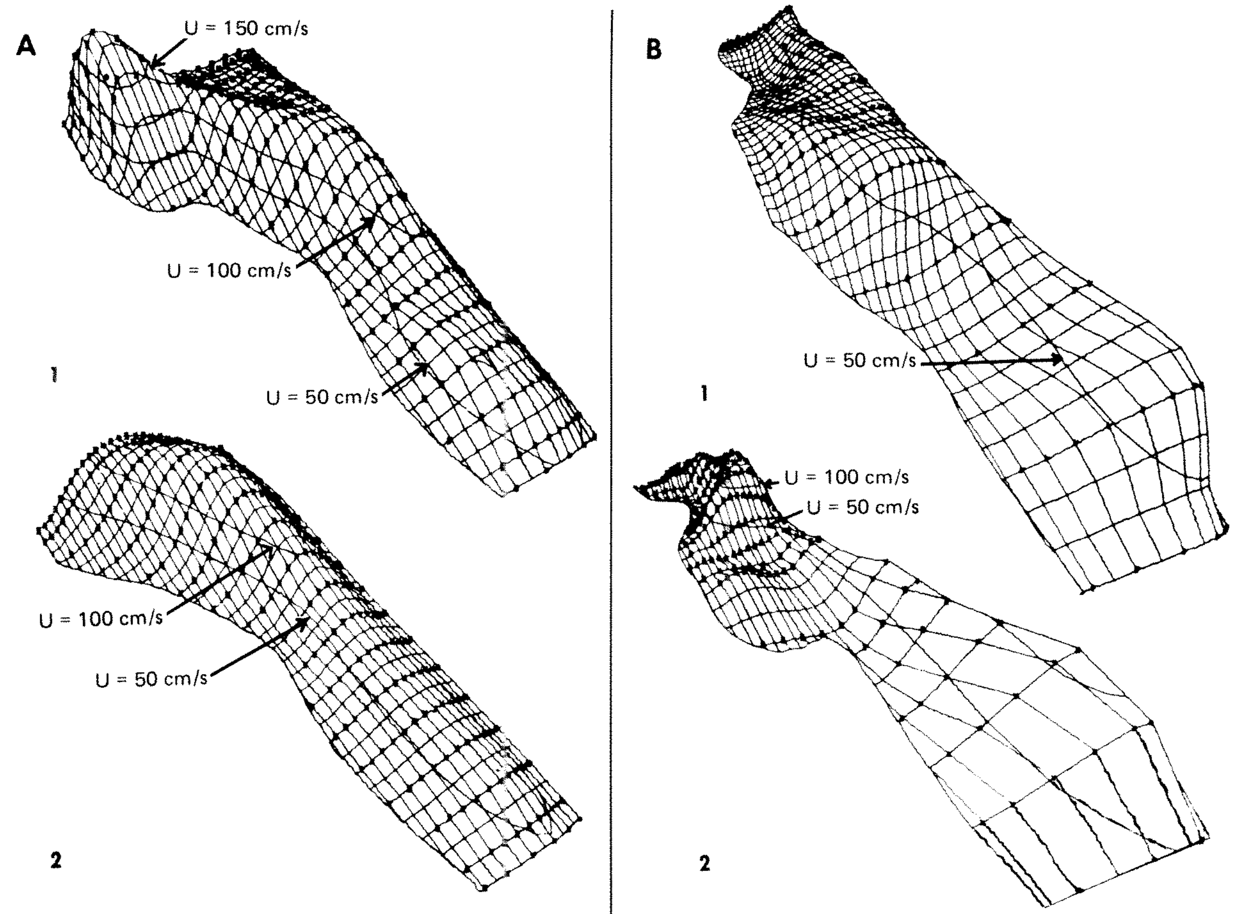
The velocity profile obtained during inspiration is reported in Figure 4B(1). This velocity field is not quite uniform and greater velocity is noted near the septum.

The velocity profile obtained during expiration is reported in Figure 4B(2). This velocity field is irregular and nonuniform. Velocity is greater in the lower portion of the section.

By comparing the velocity profile obtained in Section B during inspiration [reported in Fig 4B(1)] to the velocity profile obtained in Section D [as reported in Fig 4C(1)], one can see that the velocity field has become more uniform after the turbinate area. The turbinate area is deemed to have a streamlining effect.

Section D is located after the turbinate area during inspiration and before it during expiration. The cross section area is regularly shaped. Being three times larger than cross section E, the flow therein is three times slower than in Section E, as shown in the Table.

The velocity profile obtained during inspiration is reported in Figure 4C(1). The velocity field is generally uniform. A small area near the floor of the septum shows a greater velocity than at any other portion of this section.



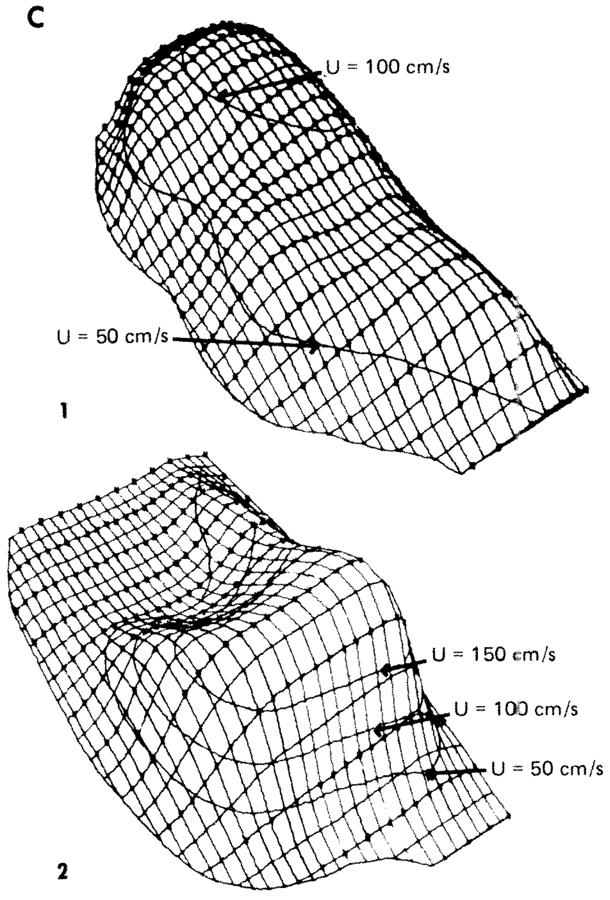


Fig 4. Velocity fields at A) Section A; B) Section B; and C) Section D. 1) Inspiration; 2) expiration.

The velocity profile obtained during expiration is reported in Figure 4C(2). The flow reaches this section after a sharp change of direction current in the nasopharynx. The change of direction creates an irregular velocity field. The greatest velocity was measured almost at the center of the section. The change of direction of flow during expiration seems particularly important in Section D because maximum velocity of 200 cm/s is reached while a maximum velocity of only 100 cm/s is obtained during inspiration. This difference is explained by the nature of the velocity fields, the inspiratory field being much more uniform than the expiratory field. In inspiration the flow has been modified by all sections of the nose including the turbinates, whereas in expiration it has been modified only by the nasopharynx and the change in direction of the airway.

The results for all Sections shown in the Table indicate that, if the criteria of flow mode inside channels used in aerodynamics are considered, the flow in the nose is mainly laminar, except in Section E (a flow is laminar if the Reynolds number is smaller than 2,100; it is in transition and turbulent if the number is greater than 2,100). Although the mean flow reported in the Table was calculated to be laminar or in transition in this study, except for Section E, strong local turbulence in velocity fields was detected by LDV, especially in areas where the velocity exceeded the mean flow. The two-dimensional velocity profile in Figure 5 and the tridimensional velocity profiles in Figure 4A-C, indicate a turbulent flow. The difference between laminar and turbulent flows in shown in the inset of Figure 5.

DISCUSSION

Characteristics of the flow of fluids in biology have been studied in relation to the effects of shapes and biological tissues. In the dolphin, the shape was demonstrated to change the boundary layer of the surrounding fluid in such a way that the flow became laminar, allowing greater speed with less energy requirement.[9] The mucus coating of the fish reduces surface tension and also allows greater speed with energy saving. Likewise, it was believed that fluid flow within the nasal fossa was influenced by geometry and biological tissues. The study of characteristics of flow of fluids within such an irregular passage as the nasal fossa was delicate. We did not use the hot-wire technique to determine velocity because it could not be precise enough due to probe-effect, and also because it was not versatile enough to obtain the numerous measurement points desired to determine velocity fields. The optical laser anemometric technique overcomes these disadvantages. On the other hand, it required a transparent wall in lieu of the septum and only half of the nasopharyngeal space. We considered that, although the experimental model did not exactly simulate biological conditions, the shortcomings were consistent in both phases of respiration, and the effects of geometry on velocity fields were valid.

Thus, this pilot study is felt to be important because not only does it demonstrate a considerable influence of shapes and dimensions on velocity fields in the nasal cavity but also because it introduces a new technique of measurement in rhinologic research.

This study substantiates the hypothesis that there are aerodynamic factors in the genesis of certain specifically located conditions such as atrophy and metaplasia of the mucosa of the septum in area 2, posterior epistaxis usually posterior to a septal deformity, carcinoma of the head of the middle turbinate in hardwood workers,[10] and pathophysiological disturbances of the communicating paranasal sinuses and eustachian tubes,[11,12] and even the inner ear.[13]

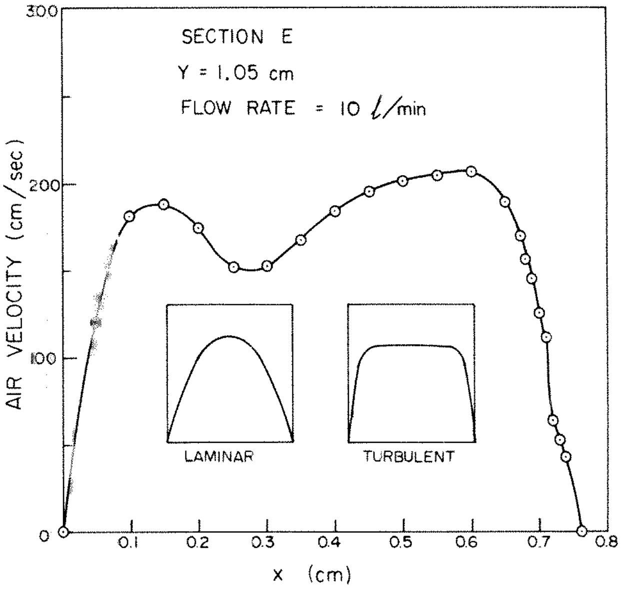


Fig 5. Typical velocity profile at Section E. Inset are general outlines of laminar and turbulent flows for reference.

Further studies should be carried out using the same technique with models simulating biological conditions as well as changes in geometry encountered in pathological noses. Since this paper was prepared, whole-organ section technique has been applied to the study of the anatomy of the nose and paranasal sinuses,[14] opening up new horizons in model reproduction.

CONCLUSION

Velocity fields obtained by computerizing data measured by laser optical anemometry in the model of a human nasal fossa showed that 1) airflow was streamlined or made more uniform by the turbinates with lower peak velocity, 2) velocity was greater near the septum, 3) the liminal valve has directional effect on flow during inspiration, and 4) flow was usually greater in the lower half of the fossa.

Although the flow obtained by calculation of the Reynolds number was laminar for the nasal fossa, the velocity fields and profiles indicated it to be turbulent.

The effect of geometry on velocity field was very striking. This was particularly evident in Section A (Fig 4A), and Section D (Fig 4C). In each section there was a marked difference between the inspiratory and the expiratory profile.

REFERENCES

1. Kern EB. Standardization of rhinomanometry. Rhinology 1977; 15:115-9.

2. McCaffrey TV, Kern EB. Clinical evolution of nasal obstruction. Arch Otolaryngol 1979; 105:542-5.

3. Girardin M. Etude expérimentale de l'écoulement d'air dans une fosse nasale. Memoire de Maitrise, Department Génie Mécanique, Ecole Polytechnique, Montréal, 1976.

4. Proetz AW. Applied physiology of the nose. St. Louis: Annals Publishing Co, 1953, Chap 6.

5. Masing H. Pathophysiology of the nasal air flow. Rhinol-

ogy 1967; 5:63-7.

6. Tos M, Magensin C. Experimental surgery of the nose, anteroposterior changes of the mucosa on altering the air flow. Rhinology 1979; 17:215-25.

7. Bilgen E, Arbour P, Trinh PT. On the resistance of airflow through the nose. American Society of Mechanical Engineers, No. 74/WA/Bio. 12.

8. Bridger GP. Physiology of the nasal valve. Arch Otolaryngol 1970; 92:543-53.

9. Schlichting H. Boundary layer theory. New York: McGraw-Hill, 1968.

10. Hadfield EH. A study of adenocarcinoma of the paranasal sinuses in woodworkers in the furniture industry. Ann R Coll Surg Engl 1970; 46:301-19.

11. Gray L. Deviated nasal septum. III - Its influence on the physiology and disease of the nose and ear. Part I. J Laryngol Otol 1967; 81:953-86.

12. McNicoll WD, Scanlon SG. The nose-ear distress syndrome. J R Nav Med Serv 1975; 61:27-9.

13. Goodhill V. Intranasal forces and labyrinthine deformations and fistulae. Rhinology 1981; 19:187-93.

14. Bridger MWM, Van Nostrand AW. The nose and paranasal sinuses — applied surgical anatomy. A histologic study of whole organ sections in three planes. J Otolaryngol 1978 Suppl 6; 7:1-33.

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ASSOCIATION OF OTOLARYNGOLOGY ADMINISTRATORS

A national association for persons who administer the business affairs of otolaryngology practice groups was established March 1, 1983, at Washington University, St Louis. The group, formally known as the Association of Otolaryngology Administrators (AOA), is an outgrowth of a meeting involving managers from a number of academic and private practice groups. The first activity of the new organization will be a national meeting October 25-26 in Anaheim, California, which coincides in part with the annual meeting of the American Academy of Otolaryngology.

The general aim of AOA is to foster professional management in otolaryngology. Strategies for achieving this objective include giving the management function greater visibility, providing appropriate educational programs, and creating a forum for the discussion of problems and the exchange of information specific to the specialty.

The need for an association which focuses on otolaryngology management results from both internal and external pressures. Internally, the scope of otolaryngology practice has broadened throughout this century and moved, in the recent past, from a field dominated by solo practice to one in which group practice is the prevalent model.

At the same time these structural changes have taken place, the nature of medical practice has changed and the management of a practice has become more complex. The physician group faces an economic problem. Does the group use its most precious resource, the time and energy of the physicians, to administer business affairs or does it focus that resource on the primary function of the group, which only physicians can perform, the practice of medicine?

As the business aspects of medical practice become more involved with social, economic, and political issues, managers and physicians need to deal with the increasing complexity by sharing information, comparing data, and developing a more complete understanding of trends in medical economics. Existing managerial organizations do not currently provide data on the specialty or a vehicle for identifying those individuals with this common interest. They do, however, provide more general information of value.

It is to fill this gap in shared information and perspectives that the AOA has been formed. Members of the executive committee are Patrick R. Connolly of the University of Iowa (Iowa City), acting president; Ruth McDaniel of Washington University (St Louis), acting secretary-treasurer; Patricia Kearney of St Louis University, acting parlimentarian; Nina S. Armstrong of The Otology Group (Nashville, Tennessee); Dean Larson of Mayo Clinic (Rochester, Minnesota); Sheri Ridge of University Otolaryngology Associates (Indianapolis); and Randall P. Wright of Baylor University (Waco, Texas).

Persons who act in a business affairs capacity in either an academic or private practice group are eligible to join the association as active members; others may join as associate members. For further information write Patrick R. Connolly, Acting President, AOA, Department of Otolaryngology-Head and Neck Surgery, University Hospitals, Iowa City, Iowa 55242.

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AUDITORY FUNCTION IN CHILDREN WITH DIABETES MELLITUS

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Fifty-one insulin-dependent diabetics and 13 nondiabetics between the ages of 8 and 21 years, without a history of exposure to noise, ototoxic drugs or ear disease, were evaluated to examine the relation between auditory function and diabetes, diabetic control and diabetic complications. Audiologic assessment included pure tone audiometry, speech audiometry, impedance measures and brainstem evoked response audiometry. No statistically significant differences in auditory function were noted between insulin-dependent diabetics and normal controls, between the diabetics in good or poor control or between diabetics with or without neurologic or vascular complications.

INTRODUCTION

A review of the literature by Axelsson et al revealed that audiologic test results of juvenile diabetics varied widely.[1] Jorgensen and Buch concluded that diabetic hearing loss was of cochlear origin because some of their subjects showed recruitment.[2] They also found a correlation between diabetic retinopathy and hearing impairment. Axelsson and Fagerberg found normal pure-tone thresholds but a minor degree of impairment in auditory function using speech, distorted speech, Bekesy audiometry, and directional audiometry.[3] They found no correlation between hearing impairment and duration or severity of diabetes mellitus. Other investigators have confirmed these results.[4-8] Marullo tested 60 diabetic patients with an extensive battery of audiometric tests and concluded that both retrocochlear and cochlear pathologies existed.[8] Friedman et al reported subclinical but widespread hearing abnormalities in diabetic patients with neuropathy.[7] They found that hearing loss occurred at many frequencies, refuting the hypothesis that diabetic hearing loss is similar to presbycusis which affects mainly the high frequencies. They speculated that hearing abnormalities were related to auditory nerve dysfunction. Osterhammel and Christau examined a group of insulin-dependent diabetics and nondiabetic patients and found no significant differences in pure-tone thresholds (250-20,000 Hz), speech reception thresholds, speech discrimination scores, or stapedius reflex thresholds between the two groups.[9] In addition, they found no significant differences in audiologic findings between those patients with and those without retinopathy. In summary, conflicting findings about the effects of and relation between diabetes and auditory function exist.

The goal of this study was to compare auditory function in young insulin-dependent diabetic subjects, with and without neuropathy, retinopathy or other diabetic complications, to auditory function in an age-matched group of normally hearing nondiabetic subjects. Children were chosen for this study so that the compounding effects of noise exposure and age on auditory function would not be as likely as in an older population. The diabetic children were closely monitored for possible progression of diabetic complications.

METHODS

Subjects. Fifty-one insulin-dependent diabetic subjects between the ages of 8 and 21 years participated in this study. All were participants in the Diabetes Registry program of the Diabetes Research and Training Center of the Washington University School of Medicine and were undergoing a three-day in-hospital evaluation as part of this program. Audiometric testing was incorporated into the studies. Thirteen nondiabetic children matched for age also underwent audiometric testing and served as controls. All studies were performed after obtaining parental consent according to protocols approved by the Human Studies Committee of the Washington University School of Medicine. None of the subjects included in the study had a history of hearing problems, ototoxic drug intake or excessive noise exposure.

Diabetes Registry Evaluation. During the three-day hospitalization, each subject's diabetic control was assessed by measurement of fasting plasma glucose, hemoglobin A_{1c} (A_{1c}) and 24-hour urinary excretion of glucose. Hemoglobin A_{1c}, hemoglobin A which has undergone irreversible post-translational glycosylation at the N-terminus of the beta chain, was measured by high-performance liquid chromatography as described by Davis et al.[10] The A_{1c} has been shown to be a reliable indicator of blood glucose control over the preceding two to three months. In our laboratory, the mean A_{1c}, expressed as percent of total hemoglobin in nondiabetics, is 6%; 95% have values below 8.4%. However, the mean, ± one standard deviation (SD), for 290 insulin-dependent diabetic subjects is 11.9% ± 2.7%, with only 6% having values below 8.4%.

Other studies performed during the evaluation included complete blood count (CBC), urinalysis, sequential multiple analysis (SMA-6/12), thyroid function tests, and a renal evaluation (including 24-hour urinary protein measurement). Fasting plasma cholesterol and triglycerides were measured. Hyperlipidemia was

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From the Central Institute for the Deaf, Department of Speech and Hearing, Washington University (Sieger, Skinner); the Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine and the St Louis Children's Hospital (White); and the Department of Otolaryngology, Washington University School of Medicine (Spector); St Louis. This investigation was supported in part by National Institutes of Health grant AM20579, by Public Health Service research grant RR00036 from the General Clinical Research Center Branch, Division of Research Facilities and Resources, Bethesda, Maryland, and by program project grant NS03856 from the National Institute for Neurological and Communicative Disorders and Stroke.

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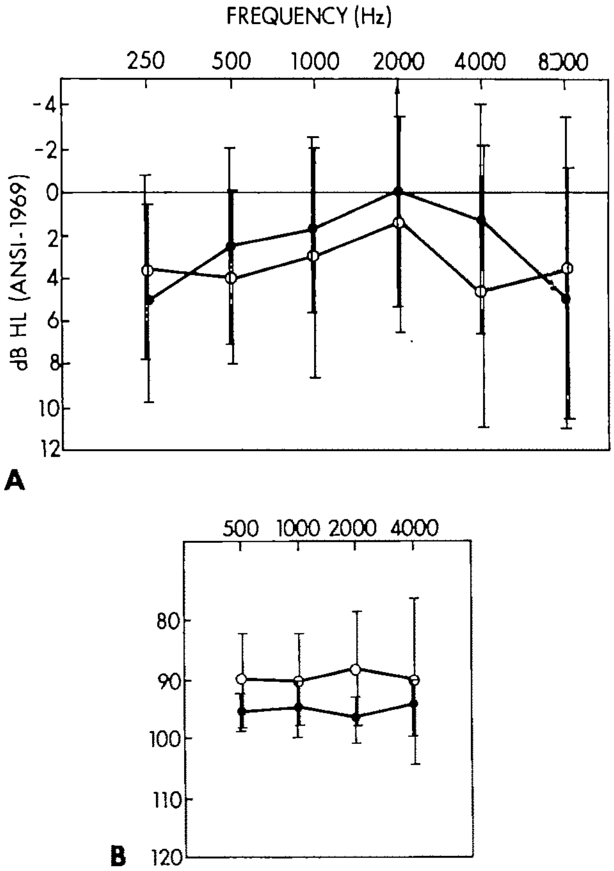

Fig 1. A) Mean pure-tone thresholds and standard deviations. B) Mean ARTs and standard deviations. ○—○ -Diabetic (N = 47); ●—● - Nondiabetic (N = 13).

defined as values above the 95th percentile for age, sex and race-matched controls according to deGroot et al.[11] Evaluation for the presence of neuropathy included a neurologic examination and nerve conduction velocity studies. Motor nerve conduction velocity was determined in the right median and right posterior tibial nerves; sensory nerve conduction velocity was determined in the right median nerve using a 2-channel electromyography (EMG) system (Disa Electronics, Franklin Lakes, NJ). Ophthalmologic evaluation for the presence of retinopathy consisted of a careful ophthalmologic examination after pupillary dilatation by an experienced ophthalmologist, and the examination of fundus photographs.

Within the group of diabetic subjects, seven had peripheral diabetic neuropathy, eight had hyperlipidemia, and ten had background diabetic retinopathy. None had proliferative retinopathy or significant proteinuria. None of the subjects had diabetes insipidus or optic atrophy.

Audiometric Testing. Audiometric testing for 47 of the diabetic subjects and the 13 normal subjects included pure-tone and speech audiometry, tympanometry, acoustic reflex thresholds (ARTs) and reflex decay.[12] Pure-tone and speech audiometry was administered in an IAC (Industrial Acoustic Co) booth with a Maico 24 audiometer using TDH-49 earphones and MX-41 cushions. The ambient noise level in the booth was 24 dBA as measured by a Bruel and Kjaer 2112 sound level meter. Speech materials (spondees, NU-6 word lists and Rush Hughes word lists) were recorded on magnetic tape and played back through a Sony TC-337 tape deck. Tympanograms, ARTs and acoustic reflex decay were measured during a Madsen Z073 impedance bridge. The Anderson test of reflex decay was used at 500 Hz and 1,000 Hz (that is, the tone was presented at 10 dB above the ART for ten seconds).

To further test the hypothesis that children with diabetes may have auditory dysfunction, eight diabetic subjects were tested using brainstem evoked response audiometry (BSER). Four of these eight subjects were not included in the audiometric testing described above. High-frequency clicks were presented at 70 dB SL to subjects via earphones. Electric responses were averaged and recorded using Nicolet CA-1000 equipment to obtain interwave latencies of Jewett waves I-V.

Data Analysis. The audiometric data were analyzed using computer program BMCP2V,[13] a repeated-measures design of the F-statistic. The subjects were divided into an older group (age 15-21 years) and a younger group (age 8-14 years), based on the assumption that ear and head configuration of young children produce slightly different hearing norms than those found in adults. Average pure-tone thresholds for the older group were compared to results of a normative study by Corso[14] while those for the younger group were compared to results obtained by Eagles et al.[15] Average pure-tone thresholds for our small nondiabetic group were not statistically different from the normative studies using larger groups of subjects and therefore appeared to be a representative sample of normally hearing subjects. They served as normal controls.

Interwave latencies for Jewett waves I-V in BSER studies were compared to those obtained by Chiappa et al.[16] Statistical analysis of data for BSER was performed using the t test. All results are reported as mean ± SD.

RESULTS

Diabetic v Nondiabetic. Analysis of the data revealed no statistically significant differences in

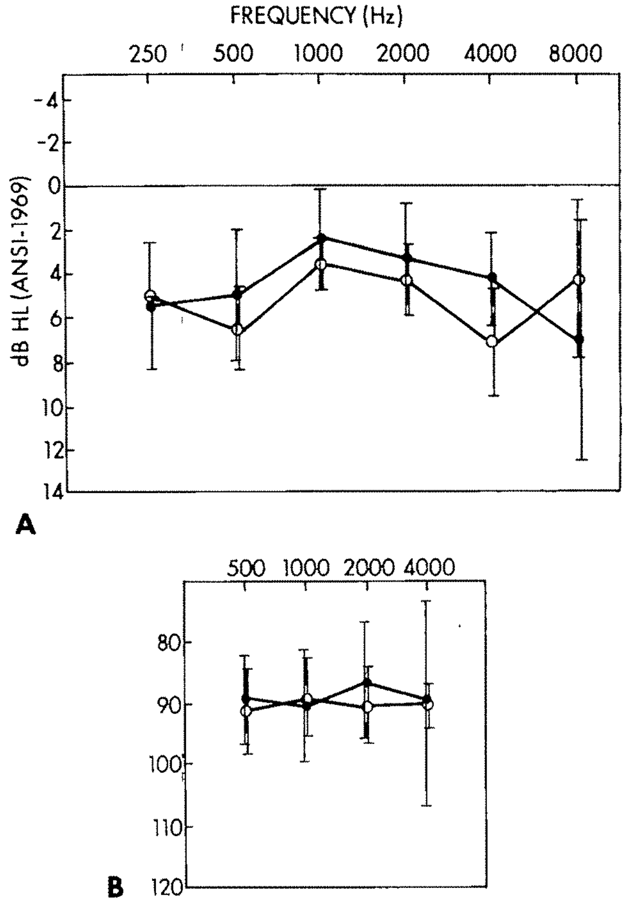

Fig 2. A) Mean pure-tone thresholds and standard deviations. B) Mean ARTs and standard deviations. ○—○ - Diabetics with neuropathy (N = 7); ●—● - Diabetics without neuropathy (N = 40).

mean pure-tone thresholds between diabetic and nondiabetic children of either age group (Fig 1A). Although no statistically significant differences were found, mean pure-tone thresholds for the diabetic group were slightly poorer at every frequency (except 250 and 8,000 Hz) than those for the nondiabetic group (Fig 1A).

There were no statistically significant differences in mean ARTs between the diabetic and nondiabetic populations. The ARTs were slightly better in the diabetic group (Fig 1B).

Relationship Between Auditory Function and Diabetic Complications. Within the diabetic population a correlation was sought between mean pure-tone thresholds and diabetic complications and between mean ARTs and diabetic complications. No statistically significant relation was found between auditory function and the presence of any of the following complications: peripheral neuropathy (defined by abnormal nerve conduction velocities, Fig 2), background retinopathy (Fig 3) or hyperlipidemia (Fig 4).

Relationship Between Auditory Function and Diabetic Control. Mean fasting plasma glucose, 24-hour urinary glucose, and A_{1C} were 206 ±70 mg/dl, 39.5±31.5 g/day and 11.8±2.5%, respectively. Four percent of our diabetic subjects had A_{1C} values below 8.4%. These results are similar to our larger population of insulin-dependent diabetics, in whom the mean A_{1C} was 11.9% and 6% had values below 8.4%. Using the arbitrary A_{1C} of 12% to separate those diabetics in poor control from those in fair-to-good control, 56% were in fair-to-good control, ($A_{1C} \leq 12\%$), and 44% were in poor control ($A_{1C} \leq 12\%$). There were no statistically significant differences in mean pure-tone thresholds and mean ARTs between diabetics in poor control and those in fair-to-good control (Fig 5). However, except at 8,000 Hz, mean pure-tone thresholds were slightly poorer in subjects with poor diabetic control (Fig 5A). Mean ARTs, except at 500 Hz, were also slightly poorer in the group with poor diabetic control (Fig 5B).

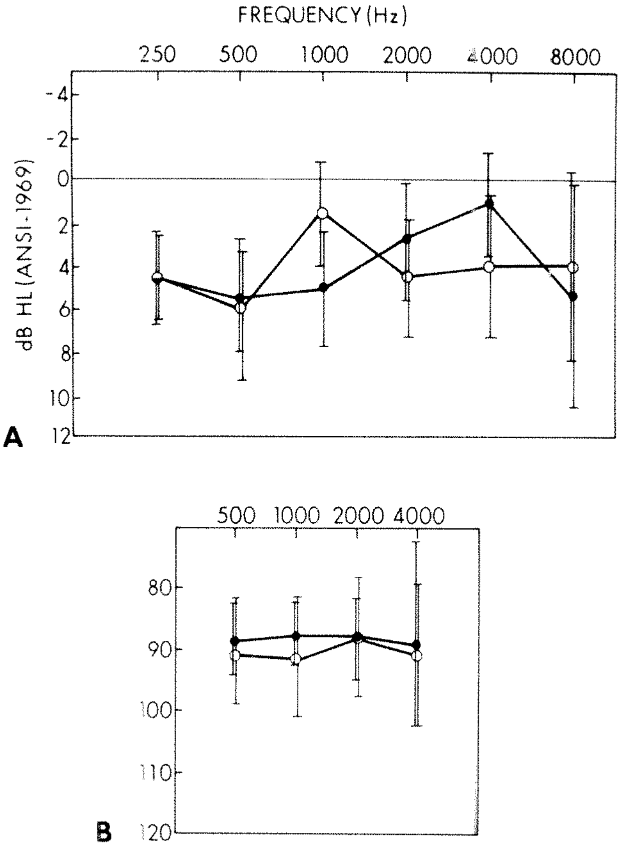

Fig 3. A) Mean pure-tone thresholds and standard deviations. B) Mean ARTs and standard deviations. ○—○ - Diabetics with background retinopathy (N = 10); ●—● - Diabetics without retinopathy (N = 37).

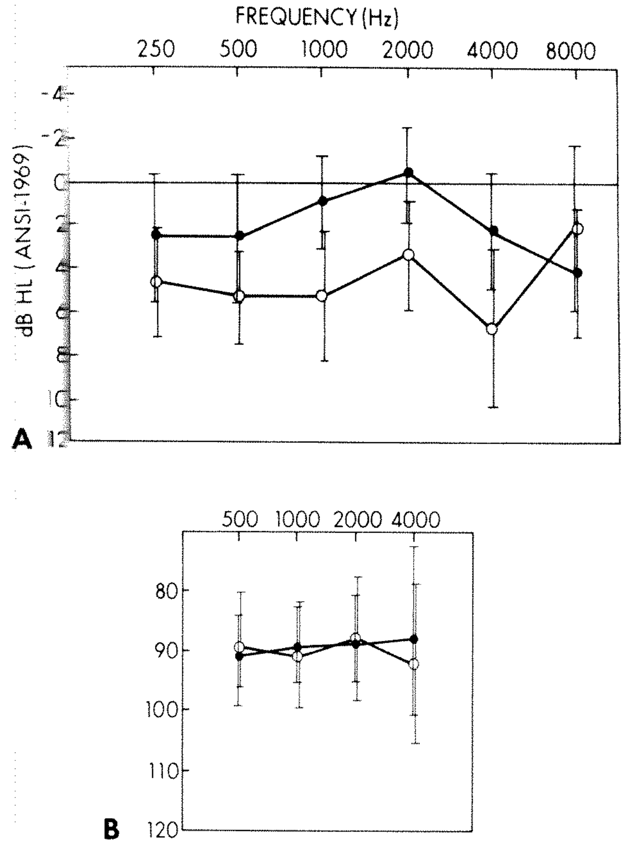

Fig 4. A) Mean pure-tone thresholds and standard deviations. B) Mean ARTs and standard deviations. ○—○ - Diabetics with hyperlipidemia (N = 8); ●—● - Diabetics without hyperlipidemia (N = 39).

Brainstem Evoked Response. The mean interwave latency for Jewett waves I-V in our insulin-dependent diabetic population was 4.02 ms, and did not differ from the mean in a normative study by Chiappa et al.[16] Interwave latencies for Jewett waves I-V were within one standard deviation of the mean in seven of eight subjects regardless of the presence of diabetic complications. Only one subject had interwave latencies (4.34 ms) that were greater than one standard deviation from the mean.

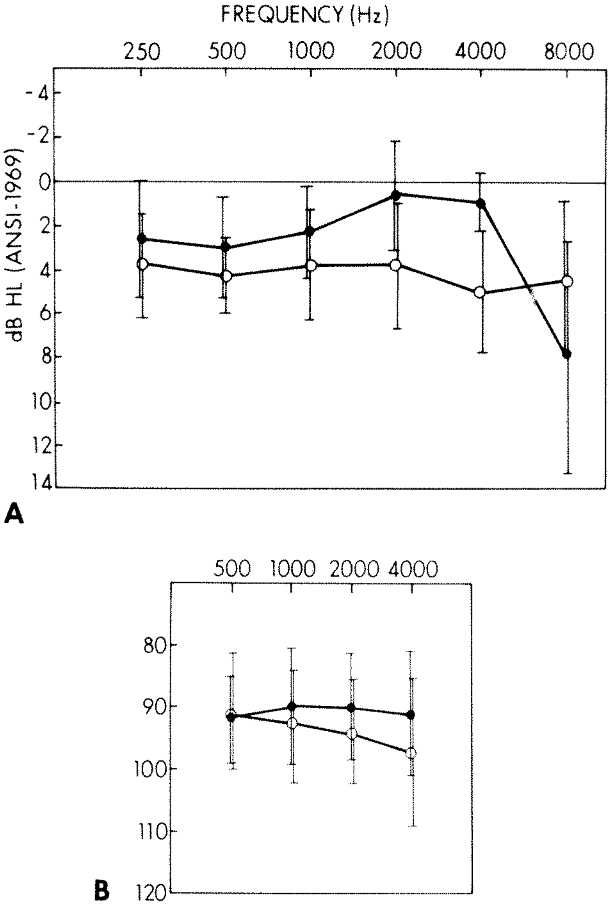

Fig 5. A) Mean pure-tone thresholds and standard deviations. B) Mean ARTs and standard deviations. ○—○ - Diabetics in poor control (N = 21); ● — ● - Diabetics in fair-to-good control (N = 26).

This patient had no detectable diabetic complications. In the only subject with peripheral neuropathy, interwave I-V latencies were within one standard deviation of the mean given by Chiappa et al.[16]

DISCUSSION

Although diabetes mellitus has been stated as a cause of hearing loss,[17] studies of auditory function in diabetic subjects have given conflicting results. Jorgensen and Buch[2] reported that 41% of 69 diabetic patients tested had hearing loss which was secondary to diabetes. However, only 5 of the 26 patients (19%) with hearing loss were free of advanced diabetic complications and were under 50 years of age. Friedman et al[7] reported a 55% incidence of sensorineural hearing loss in 20 diabetics between the ages of 22 and 70 years with well-established peripheral neuropathy. Some of these subjects were over 50 years of age, and many were not insulin-dependent. In contrast, Axelsson et al,[1] Osterhammel and Christau[9] and Aantaa and Lehtonen[18] failed to demonstrate abnormalities in hearing among diabetic subjects regardless of duration of diabetes or the presence of diabetic complications, but found abnormalities only after the appearance of severe microangiopathic complications. One problem with many of these reports is the diversity of the diabetic groups studied. Subjects included both young and old patients with varying degrees of diabetic complications ranging from complete absence to the presence of severe, life-threatening complications. For most of these studies the presence or absence of diabetic complications was determined clinically but not by sensitive biochemical and physiological parameters. Little or no attention was paid to the correlation of auditory dysfunction with sensitive measures of diabetic complications. Specifically, peripheral nerve conduction velocity data were absent. Although severe complications of diabetes mellitus, such as proliferative retinography, neuropathy and nephropathy, occur in only about 30% to 50% of diabetic subjects,[19] milder subclinical forms of complications are more common and, at present, easily identified.[20]

The present study was undertaken to determine whether young insulin-dependent diabetics had evidence of auditory dysfunction, and whether or not any such auditory dysfunction could be correlated with sensitive techniques for determining the presence or absence of diabetic complications or with the degree of diabetic control.

No significant abnormalities of auditory function were found in the group of 51 young insulin-dependent diabetics studied. Although none of these subjects had advanced forms of microangiopathic complications, seven had abnormal peripheral nerve conduction velocities and ten had background diabetic retinopathy. There was no apparent correlation between auditory function and these mild forms of diabetic complications. Furthermore, there was no correlation between auditory function and diabetic control.

Although no significant abnormalities were detected in the present study, conclusive evidence that insulin-dependent diabetes mellitus has no effect on auditory function over long periods of time is still lacking. Most diabetic complications increase in incidence with increasing duration of diabetes;[19] the subjects in this study had diabetes mellitus only for a short time (1 to 6 years). In addition, the test performed in this and most previous investigations of hearing in diabetics may not be sensitive enough to detect mild abnormalities which might precede more severe, clinically apparent hearing losses. Long-term prospective studies of auditory function in a larger number of insulin-dependent diabetic subjects are needed to evaluate fully the possible association between diabetes mellitus and auditory function. These studies should include a careful classification of the diabetic disease and careful monitoring for complications. In addition, these studies should include more sensitive measures of the presence of complications, such as peripheral nerve conduction velocity studies, fluorescein angiography and vitreous fluorophotometry. Furthermore, consideration should be given for including tests of auditory function which are more sensitive and give further information to site-of-lesion.

Although our initial attempt to use BSER audiometry failed to show significant alteration in latency of auditory pathway responses, the number of subjects studied was far too small to be conclusive. Further investigations should include more subjects in this area.

ACKNOWLEDGMENT — We are indebted to Dr Edward Spitznagel for performing the statistical evaluation of the data, to Dr David W. Meltzer for the ophthalmologic evaluations and to Mrs Jean Mayo for secretarial assistance in the preparation of the manuscript.

REFERENCES

1. Axelsson A, Sigroth K, Vertes D. Hearing in diabetics. Acta Otolaryngol (Stockh) 1978; Suppl 356:2-23.
2. Jorgensen MB, Buch NH. Studies on inner ear function and cranial nerves in diabetics. Acta Otolaryngol (Stockh) 1961; 53: 350-64.
3. Axelsson A, Fagerberg SE. Auditory function in diabetics. Acta Otolaryngol (Stockh) 1968; 66:49-64.
4. Marshak G, Anderson CV. Bekesy audiometry with juvenile onset diabetes. J Aud Res 1968; 8:323-30.
5. Rosen Z, Davis E. Microangiopathy in diabetics with hearing disorders. Ear Nose Throat Monthly 1971; 50:479-82.
6. Roach RE. Response of the diabetic to Bekesy audiometry. Arch Otolaryngol 1973; 98:218-29.
7. Friedman SA, Shulman RH, Weiss S. Hearing and diabetic neuropathy. Arch Intern Med 1975; 135:573-6.
8. Marullo T. Contribution a letude des hypoacousies perceptives du diabete sucre. Rev Laryngol 1974; 95:253-71.
9. Osterhammel D, Christau B. High frequency audiometry and stapedius muscle reflex thresholds in juvenile diabetics. Scand Audiol 1980; 9:13-8.
10. Davis JE, McDonald JM, Jarrett L. High performance liquid chromatography method for HgbA1C. Diabetes 1978; 27: 102-7.
11. DeGroot I, Morrison JA, Kelly KA, et al. Lipids in school children 6-17 years of age: upper normal limits. Pediatrics 1977; 60:437-43.
12. American National Standards Institute. Specifications for audiometers. ANSI S3.6-1969. New York: American National Standards Institute, 1970.
13. Dixon WJ, Brown MB. BMPD-79, Biomedical Computer Programs, P-Series. Los Angeles: University of California Press, 1979.
14. Corso JF. Age and sex differences in pure-tone thresholds. Arch Otolaryngol 1963; 77:385-405.
15. Eagles EL, Wishik SM, Doerfler LG. Hearing sensitivity and ear disease in children: a prospective study. St. Louis: Laryngoscope Press, 1967.
16. Chiappa KH, Gladstone KJ, Young RR. Brainstem auditory evoked response: studies of waveform variations in 50 normal human subjects. Arch Neurol 1979; 36:81-7.
17. Meyerhoff W, Liston S. Metabolism and hearing loss. In: Paparella M, Shumrick D, eds. Otolaryngology. Vol 2. 2nd ed. Philadelphia: WB Saunders, 1980:1835-6.
18. Aantaa E, Lehtonen A. Electronystagmographic findings in insulin-dependent diabetics. Acta Otolaryngol (Stockh) 1981; 91:15-8.
19. Felig P. Disorders of carbohydrate metabolism. In: Bondy PK, Rosenberg LE, eds. Metabolic control and disease. Philadelphia: WB Saunders, 1980:276-392.
20. White NH, Witt MF, Meltzer D, Tollefsen S, Palmberg P, Santiago JV. Onset of diabetic complications during childhood. Read before the Society for Pediatric Research, Washington, DC, May 11-14, 1982.

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A postgraduate course in basic review and recent advances in neuroradiology and head and neck radiology will be held at the Copley Plaza Hotel in Boston, Massachusetts, on September 26-30, 1983. The program chairman is Juan M. Taveras, MD, and the program directors are Kenneth R. Davis, MD, and Alfred L. Weber, MD. For further information contact Harvard Medical School, Department of Continuing Education, Boston, MA 02115 (617) 732-1525.

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BASOPHILIC DEPOSITS IN THE STRIA VASCULARIS

A CLINICOPATHOLOGICAL UPDATE

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BEIRUT, LEBANON

Basophilic deposits in the stria vascularis have been found in association with a multitude of disease entities. Their true significance and nature remain obscure. In the temporal bone collection at the Massachusetts Eye and Ear Infirmary are 22 cases with basophilic deposits in the stria vascularis. The ages of the subjects studied ranged from two days to 83 years. Atrophy of the stria vascularis was the main pathology seen in their temporal bones. The deposits were found in both ears in 82% of cases. They tend to show a striking polymorphism. Special histochemical stains suggest they contain glycogen. Hypertension and uremia were two health problems most of the subjects were suffering from during life. A theory is advanced as to the immune complex nature of these deposits. A review of the literature concerning this subject is also offered.

REVIEW OF THE LITERATURE

The earliest available report concerning abnormal deposits in the stria vascularis dates back to 1906 when Goerke[1] described "cystic formations and spherical hyaline aggregates in the stria vascularis" of a patient with congenital deafness and retinitis pigmentosa. In 1927, Nager[2] described a similar entity. In 1934, Rollin[3] reported on basophilic deposits in the stria vascularis in normal-hearing individuals and labeled them as calcium deposits. Yamakawa[4] in 1938, labeled these as "phleboliths in a case of Menière's disease." Later in 1950, Altmann[5] called these deposits calcified thrombi in capillary endothelia. In 1954, Lindsay and Hemenway[6] reported on "amorphous exudates that overlie an inflammatory focus in a partially missing stria." In 1958, Keleman[7] described "aggregates" in the stria vascularis of a 3-week-old infant with toxoplasmosis. He thought they were calcific deposits. In that same year Hinojosa,[8] in a study of the temporal bones of the progeny of a mother with pseudohypoparathyroidism, described calcific deposits in the stria vascularis and spiral ligament and suggested they were "end-products of a disturbed calcium metabolism." Further support for this last theory was the presence of these deposits in the stria vascularis in cases of otosclerosis, Paget's disease, and toxoplasmosis. Hypervitaminosis D has also been incriminated. In a temporal bone study of three patients with the cardioauditory syndrome of Jervell and Lange-Nielsen, Friedman et al[9] in 1966 reported on large deposits of PAS+ material in the stria vascularis suggesting they might contain mucopolysaccharides or allied substances. In another report[10] in 1968, they thought the deposits had a fibrinoid consistency.

The first detailed histochemical study on these deposits came from Nomura and Mori[11] in 1968 when they reported on the temporal bone findings in an infant with hypophosphatasia. This tissue was PAS+, did not show metachromasia with toluidine blue, stained blue with azan stain, and gave no reaction to Hale's colloid iron stain. The authors thought that these deposits might be pathognomonic of the disease. Reporting on four of their cases with strial concretions in 1973, Naunton and Lindsay[12] claimed these concretions to be "the product of a degenerative process of genetic or acquired origin."

More recent reports reveal a striking association of these deposits with chronic renal disease and hemodialysis.[13-15]

MATERIALS AND METHODS

Over 1,000 temporal bones of the collection at the Massachusetts Eye and Ear Infirmary were screened and a total number of 22 cases (2%) could be documented as having basophilic deposits in the stria vascularis.

All subjects were studied according to the following protocol: age, sex, primary otological diagnosis, systemic diagnosis and cause of death. The temporal bones, with particular reference to strial pathology were studied, and the available medical records of every patient were reviewed. All pertinent data with a possible bearing on the etiology of these deposits were recorded. They were then analyzed with the idea of correlating the findings with the presence of the deposits.

RESULTS

AGE AND SEX

Figure 1 shows the age distribution of the subjects at the time of death. The youngest patient in the series was 2 days old at the time of death and the oldest was 83. Seven patients were under 10 years of age and another seven fell within the eighth decade. There is a noticeable gap in young adults and middle age groups. There were 16 males and six females.

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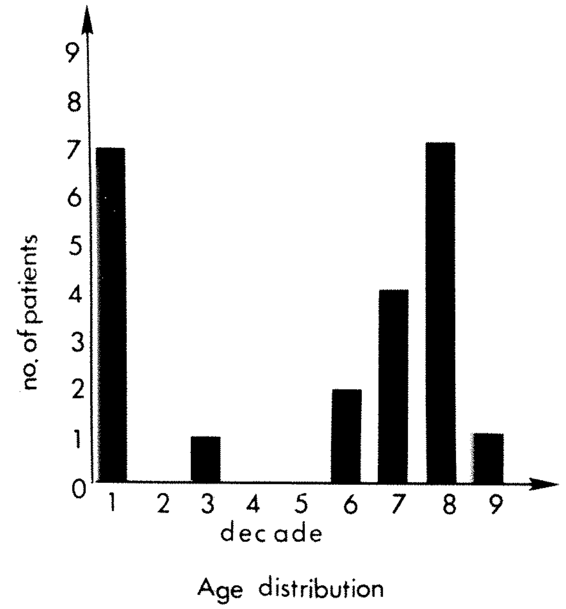

Fig 1. Age distribution of 22 subjects with strial deposits.

CAUSE OF DEATH

The causes of death were arbitrarily subdivided as shown in Table 1. The deaths of two of the subjects were undocumented. Central nervous system and pulmonary disorders are the leading causes of death in this series.

PRIMARY OTOLOGICAL DIAGNOSIS

The diagnosis was set according to the patient's otological work-up prior to death and to postmortem temporal bone findings (Table 2). It sounds reasonable that only a few of these patients have a "pure" primary otological diagnosis with the vast majority having mixed pathologies.

SYSTEMIC DIAGNOSIS

Health problems of the subjects were subdivided and grouped according to involvement of major organ systems and malignancy (Table 3). Six of the subjects are listed under "others" in accordance with the diagnosis appearing in the autopsy report.

Histopathological evaluation of the 42 temporal bones belonging to the 22 subjects (two left ears were not available in the series) revealed the following observations:

Condition of the Stria Vascularis. Two main pathologies were seen in the stria vascularis. Strial atrophy was seen in 12 of the 22 subjects (54.5%). Evidence of substrial fibrosis was seen in three subjects (13.7%). The stria appeared normal in seven subjects (32%). There were four subjects with cystic formations.

TABLE 1. CAUSE OF DEATH

	No. of Patients
Central nervous system disorders	6
Respiratory failure	6
Cardiovascular failure	3
Malignant tumor	3
Renal failure	1
Peritonitis	1
Undetermined	2
Total	22

TABLE 2. CLASSIFICATION OF PATIENTS ACCORDING TO PRIMARY OTOLOGICAL DIAGNOSIS

	No. of Patients
Strial presbycusis	6
Primary neural degeneration	4
Infection in temporal bone	3
Cerebellopontine angle malignancy	1
Internal auditory canal malignancy	1
Hereditary inner ear degeneration	1
Congenital deafness	1
Premature atrophy of spiral ligament	1
Dysequilibrium of aging	1
Cupulolithiasis	1
Histiocytosis-X (Letterer-Siwe's disease)	1
Normal	1
Total	22

Unilateral v Bilateral Deposits. Eighteen subjects (82%) have deposits in both temporal bones. Two had them in one temporal bone and two left temporal bones were not available for comparison.

Spiral Ligament. Fifteen subjects (68%) had normal spiral ligaments bilaterally, while only 7 (32%) had evidence of atrophy of varying degrees ranging from decreased cellularity, consistent with age, to severe degeneration and/or fibrosis.

Location of the Deposits in the Cochlea. The deposits were not localized to one specific cochlear turn, but tended in the vast majority of cases to extend over two and even all three turns. The middle turn was the most common location followed in frequency by the basal turn and apical turn.

Location of the Deposits in the Stria Vascularis. The majority of deposits in the stria vascularis appear in the marginal zone of the stria vascularis and protrude into the endolymphatic space (Fig 2). The bulk of the deposits occupy the middle one third of the stria vascularis (Fig 3). This was determined

TABLE 3. SYSTEMIC DIAGNOSIS

	No. of Patients
Cardiovascular disease	5
Malignant neoplasm	5
CNS disease (intracranial hemorrhage, seizure, etc)	4
Pulmonary diseases	2
Others	
Cretinism	1
Neonatal myotonic dystrophy	1
Alport's syndrome	1
Hypophosphatasia*	1
Appendicitis	1
Histiocytosis-X	1
Total	22

*Findings in this case were reported previously.[11]

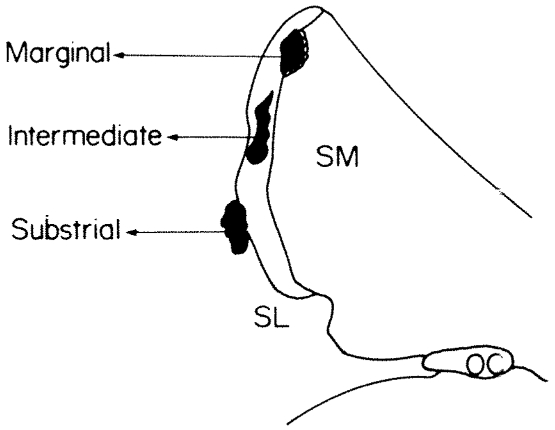

Fig 2. Distribution of deposits in layers of stria vascularis. RM - Reissner's membrane; SM - Scala media; OC - Organ of Corti; SL - Spiral ligament.

during histological examination of serial horizontal sections.

The deposits, as they appear on histological sections, tend to show different "shades of blue" indicating intensity of staining with hematoxylin and eosin stain. They were also labeled as large, medium, and small. This was done by measuring the largest space they occupy in the stria vascularis in one histological section. Strial pathology, size of the deposit, and its intensity of staining were then studied in relation to each other (Table 4). It is clear that there is no relation between severity of the strial atrophy and size and intensity of staining of the deposits. In most cases, the organ of Corti showed some form of pathology ranging from mild loss of hair cells to severe and/or total degeneration.

ANALYSIS OF DATA

The age distribution of the patients denotes either a congenital or hereditary etiology or a degenerative, age-related process. This is in agreement with other series which report deposits in subjects at extremes of age. It is not known whether the male predominance is significant.

The great variety of organ system disorders in these cases speaks against a possible etiological relationship to the strial deposits. The possibility of these deposits being an agonal phenomenon is unlikely; the longest postmortem period before temporal bones were fixed was 22 hours.

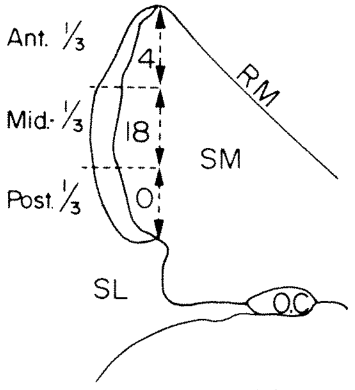

Fig 3. Anteroposterior distribution of deposits in the stria vascularis.

TABLE 4. RELATION OF STRIAL PATHOLOGY TO SIZE AND DEPTH OF STAINING OF STRIAL CONCRETIONS

Condition of Stria	*No. of Concretions*	*S*	*M*	*LA*	*LI*	*D*	*B*
Normal	6	3	1	2		5	1
Mild atrophy	2	2				2	
Moderate atrophy	4	1	3		2	1	1
Severe atrophy	7	1	6		2	1	4
Substrial fibrosis	3	1	1	1		3	
Total	22						

S - Small. M - Medium; LA - Large; LI - Light; D - Dark; B - Both.

PRIMARY OTOLOGICAL DIAGNOSIS

Strial atrophy, primary neural degeneration, and infection account for more than half of the primary otological diagnoses. The temporal bone series at the Massachusetts Eye and Ear Infirmary includes 33 subjects with the primary diagnosis of strial atrophy, six of which had strial deposits (18%). Histologically, the deposits found in these striae are not different from the others. The incidence of strial deposits is 4% in the same temporal bone series with the diagnosis of primary neural degeneration and only 1% in temporal bone infections. In these cases, strial atrophy also seems to be the predisposing factor for the formation of deposits.

YOUNG SUBJECTS

Six subjects (12 temporal bones) show normal-appearing striae vascularis. Only one shows evidence of atrophy. However, three show an unusually severe and unexplained spiral ligament atrophy with substrial fibrosis. One of the subjects had "otologically normal" temporal bones. Another patient who died from cardiorespiratory failure secondary to neonatal myotonic dystrophy had severe atrophy of his spiral ligament and, among all other patients, had the largest and deepest staining deposit. Was the pathological process more severe in this case? Letterer-Siwe disease, cretinism, hypophosphatasia, Scheibe's dysplasia, bilateral internal auditory meatus malignancy, astrocytoma of pons, and osteopetrosis are other diagnoses included in this group and, again, show large and deep staining deposits in the striae vascularis. They also point to their multifactorial etiology.

HISTOLOGICAL CONSIDERATIONS

The deposits show a striking polymorphism (Figs 4-9). Some are elongated or crescent shaped. Others appear more rounded or polygonal with a concentric lamellar pattern. Still others exhibit a fibrillar pattern reminiscent of the "sunray appearance."

Cyst-like formations in the stria vascularis contain clumps of these deposits that, at times, seem to coalesce and form larger ones. Few sections show

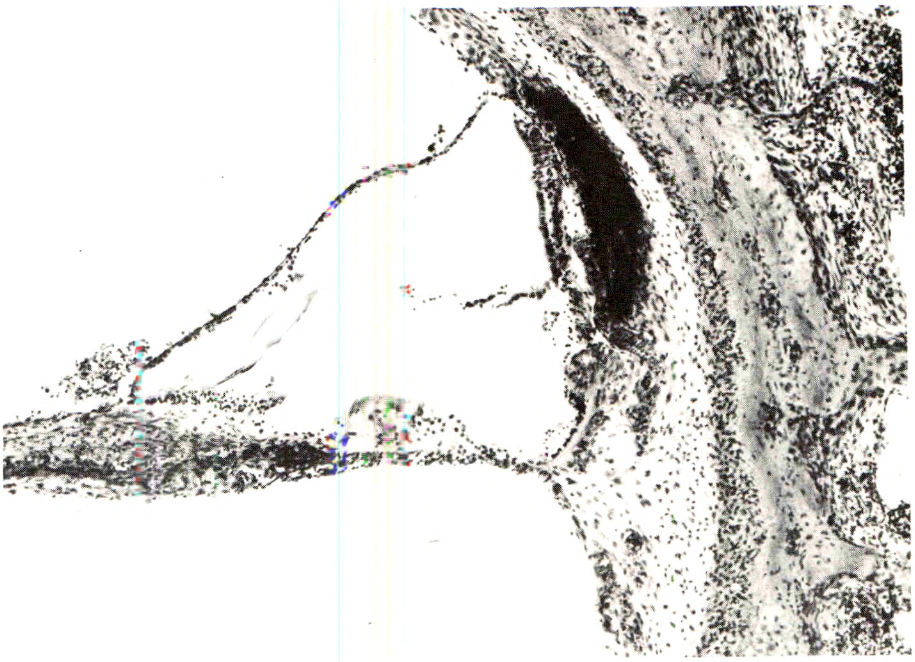

Fig 4. (Patient 1, baby with diagnosis of hypophosphatasia) Middle turn of cochlea. Stria vascularis shows evidence of atrophy. Large, deeply stained basophilic deposit almost totally replaces atrophied stria which seems to be "peeling off" spiral ligament. (Courtesy of Dr Y. Nomura, Tokyo)

these deposits causing the stria vascularis to bulge and peel off the spiral ligament. Though quite diverse in appearance, these deposits present some pecularities common to all of them.

1. Aggregates of pigment material (lipofuscin, melanin) seem to "hug" these deposits. Lipofuscin is known to be a byproduct of cellular degeneration.

2. Proximity of the deposits to blood vessels. Although this was described before, the significance is questionable since we are already dealing with a highly vascular structure.

3. Proximity to aggregates of cells with pyknotic nuclei and deeply basophilic suggests a degenerative deposit taking place.

4. Seven of the deposits show a crystalline pattern with sharp edges and fine spicules. This was previously described by Nadol[16] in a case of longstanding profound sensorineural deafness. The deposit he describes had a "crystalline substructure." He also related it to the metabolic abnormalities associated with the patient's chronic renal failure or, more simply, to atrophy of the stria vascularis in this case.

SPECIAL HISTOCHEMICAL STUDIES

Representative temporal bone sections from seven patients belonging to the subgroups mentioned under primary otological diagnosis were stained with PAS and alcian blue reinforced with

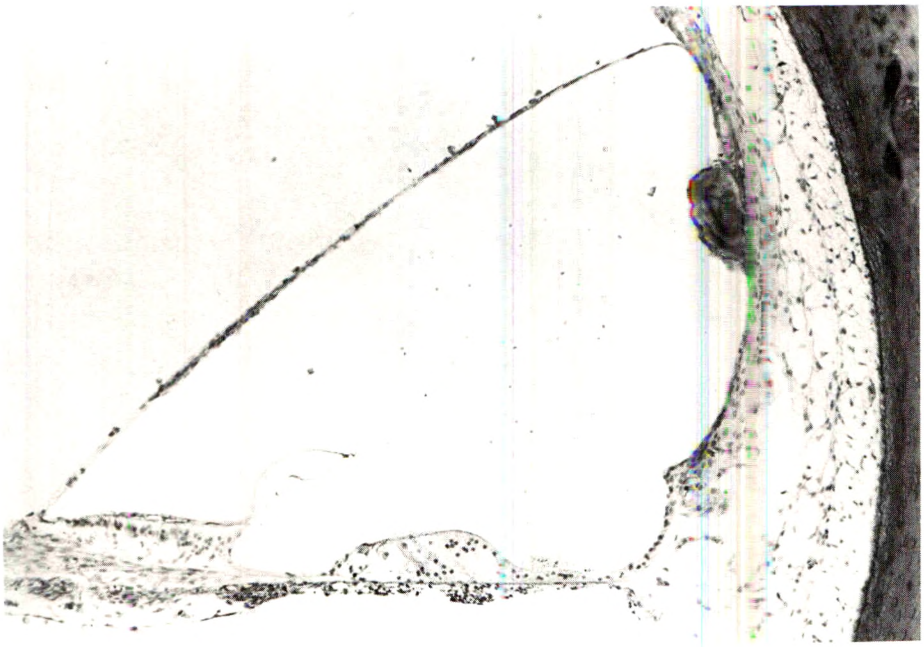

Fig 5. (Patient 2, age 54) Death of suppurative meningitis secondary to labyrinthitis and chronic otitis media. Basal turn of cochlea shows severe atrophy of stria vascularis with medium-sized basophilic deposit with concentric, lamellar layers of different density.

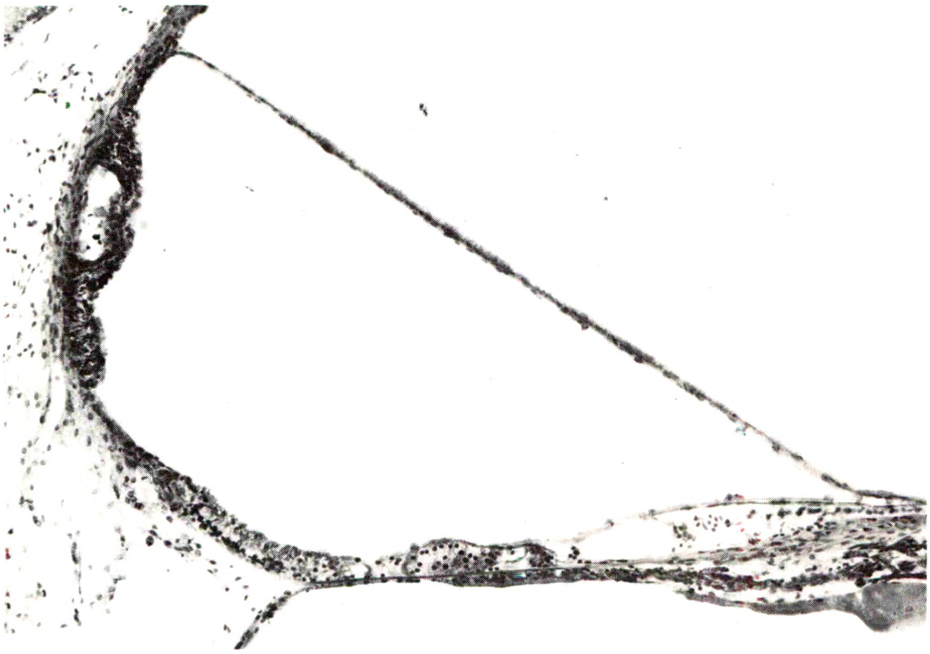

Fig 6. (Patient 3, age 83) Death of intracerebral hemorrhage. Primary otologic diagnosis was strial atrophy. Section through basal turn of left ear shows cystic formation in stria vascularis with small scattered deposits within cyst.

hematoxylin and eosin. Acid mucopolysaccharides, connective tissue, goblet cells and microbial capsules take on a bright turquoise blue stain with alcian blue while glycogen, glycoproteins and other associated chemical substances take on a magenta blue color with PAS.

Two patients with strial atrophy and one patient each with premature atrophy of spiral ligament, hypophosphatasia, temporal bone infection, temporal bone malignancy and Alport's syndrome were selected. All deposits were PAS+ except the one belonging to the hypophosphatasia group and one with strial atrophy.

None took the alcian blue stain. This suggests that the deposits are glycogen-like and are devoid of connective tissue. The nonstaining of the deposits in the stria vascularis of the baby with hypophosphatasia with PAS may denote a different nature and composition of this particular deposit. This, however, is not in agreement with Nomura's findings of a PAS+ deposit in the stria vascularis of a patient with hypophosphatasia.

ANALYSIS OF PAST MEDICAL HISTORY

The medical records of these subjects show a variety of health problems (Table 5). Hypertension and uremia are the most frequent systemic diagnoses associated with strial deposits. Intake of ototoxic drugs, jaundice, radiotherapy and anemia were also frequently present.

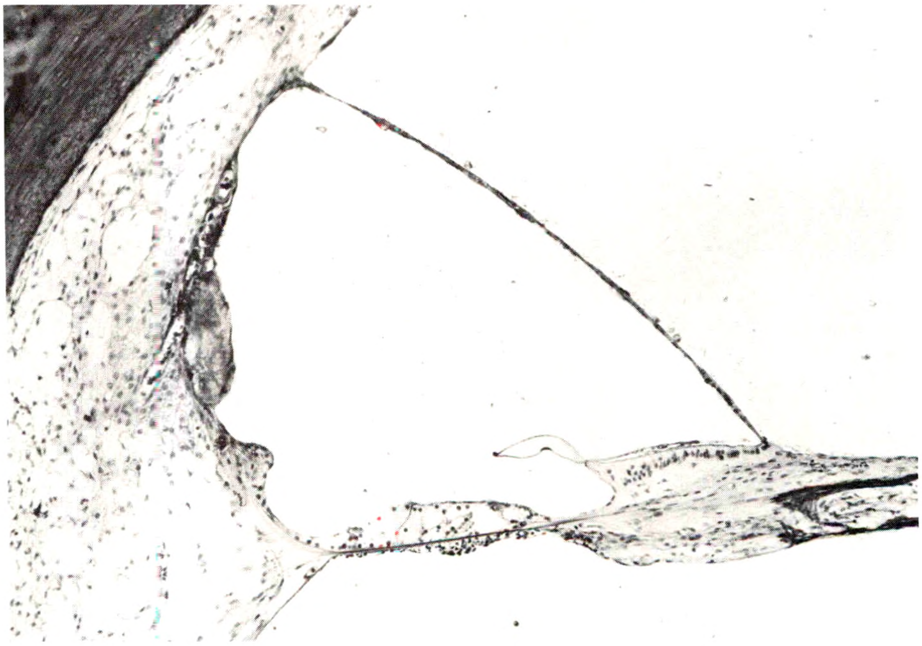

Fig 7. (Patient 2) Photomicrograph of middle turn of cochlea showing rather large basophilic deposit in moderately atrophied stria vascularis. Striking proximity to blood vessel and "sunray appearance" of fine fibrillar network of deposit are obvious.

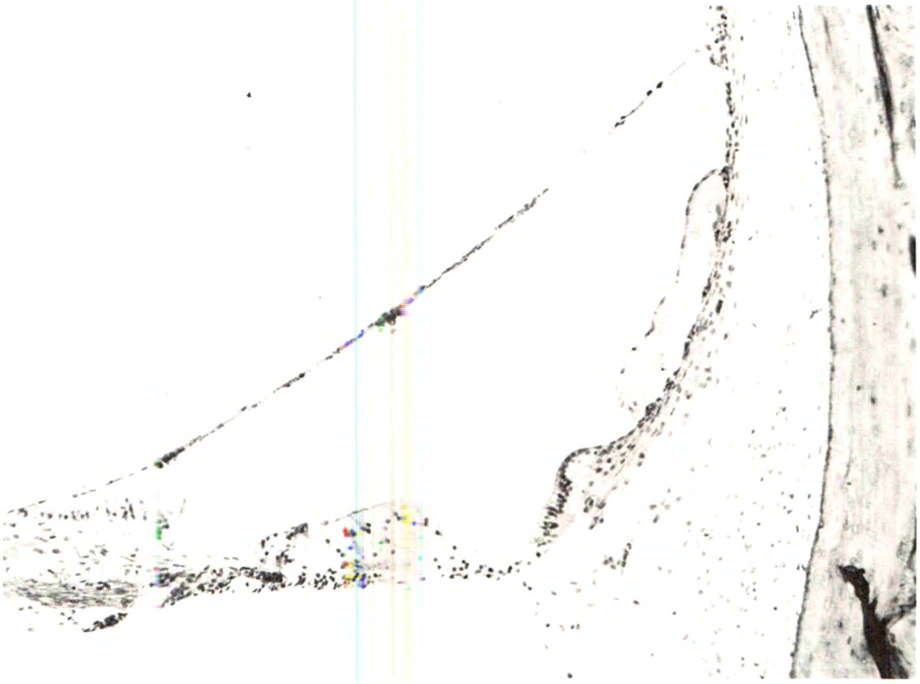

Fig 8. (Patient 4, age 72) Cause of death given as acute myocardial infarction. Primary otologic diagnosis was strial atrophy. Section shows middle turn of cochlea showing severe strial atrophy with pale stained basophilic deposit in middle one third of stria vascularis.

Among the previously listed entities, uremia deserves special attention. Bergstrom et al[13,14] and Oda et al[15] describe basophilic deposits in the stria vascularis of patients with chronic renal failure. Oda et al found them in all temporal bones of patients who underwent renal transplant. Thus, the accumulated data concerning the presence of stria vascularis deposits in patients with chronic renal failure suggest a strong cause and effect relationship.

COMMENT

The numerous theories that have been advanced to explain the nature of basophilic deposits in the stria vascularis certify to their still unknown etiology and physiochemical composition. Interesting correlations with some disease entities were found and are in agreement with previously reported conditions. Some new associated conditions were, however, found. The association with chronic renal failure seems to be strong. Could some of the deposits in our series actually be immune complex deposits?[15] This seems likely, particularly in view of the fact that we are dealing with a vascular tissue in many respects similar to other tissues in the body (eg, with kidney) where immune complex deposits were found. This fascinating theory has still to be substantiated.

We would like to raise these other questions: Why weren't these deposits ever found in the scala

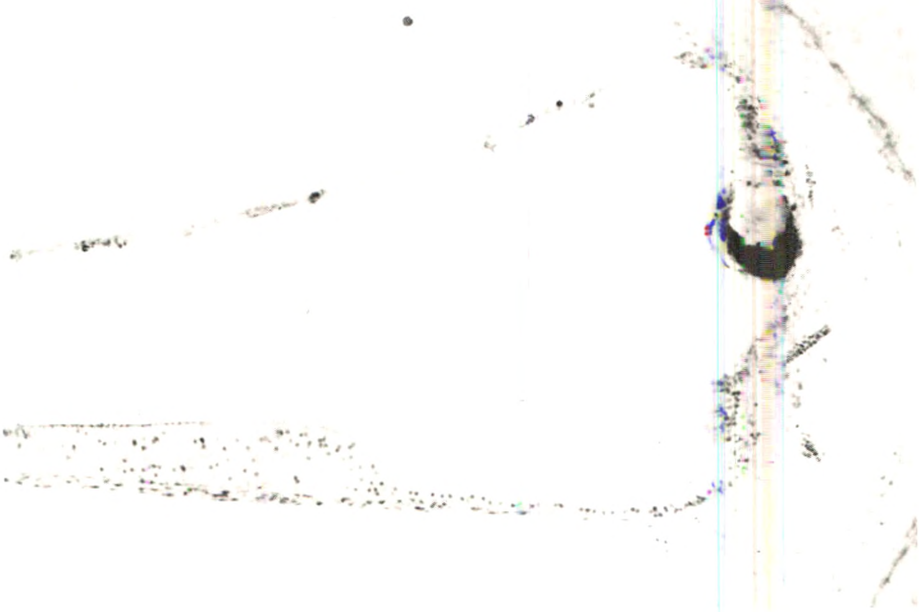

Fig 9. (Patient 4) Section shows middle turn of cochlea with basophilic deposit in severely atrophied stria vascularis. Deposit shows variable densities of staining.

TABLE 5. MEDICAL HISTORY

	No. of Patients
Hypertension	7
Uremia	7
Aminoglycosides intake	5
Jaundice	4
Radiotherapy	4
Anemia	3
Alcoholism	2
Diabetes mellitus	2
Bleeding disorders	1
Gout	1

media despite a very thin attachment to the marginal zone of the stria? Could the clue to their nature be found in the chemical composition of endolymph? What is the significance of their presence in an otologically normal individual? And, finally, how do they help us understand ear disease and prevent it? The answers are still unknown. Further histochemical and ultrastructural studies are needed to elucidate the nature of these puzzling deposits.

SUMMARY

The results of a study of 42 temporal bones with basophilic deposits in the stria vascularis were presented. These deposits were found in a wide variety of seemingly different disease entities. Atrophy of the stria vascularis is, however, the pathological correlate found in the majority of subjects studied.

It also appears that they have more than one chemical composition, with glycogen being one. They were significantly present in subjects with previous history of uremia and hypertension. Their presence in young and elderly subjects hints to their congenital and/or degenerative etiology. A review of the literature concerning this subject was done.

REFERENCES

1. Goerke M. Zwei Fälle angeborener Taubstummheit. In: Dender A, ed. Die Anatomie der Taubstummheit. Wiesbaden: JF Bergmann, 1906:21-35.

2. Nager FR. Zur Histologie der Taubstummheit bei Retinitis pigmentosa. Beitr Pathol Anat 1927; 77:288-303.

3. Rollin H. Über Kalkablegerungen in der Stria vascularis der Labyrinthes. Arch Klin Exp Ohren Nasen Kehlkopfheilkd 1934; 138:1-5.

4. Yamakawa K. Über die pathologische Veränderung bei einem Ménière-Kranken. Z Oto-rhino-laryngol 1938; 34:180-1.

5. Altmann F. Histologic picture of inherited nerve deafness in man and animals. Arch Otolaryngol 1950; 51:852-90.

6. Lindsay JR, Hemenway W. Inner ear pathology due to measles. Ann Otol Rhinol Laryngol 1954; 63:754-71.

7. Keleman G. Toxoplasmosis and congenital deafness. Arch Otolaryngol 1958; 68:547-61.

8. Hinojosa R. Pathohistological aural changes in the progeny of a mother with pseudohypoparathyroidism. Ann Otol Rhinol Laryngol 1958; 67:964-71.

9. Friedmann I, Fraser GR, Froggatt P. Pathology of the ear in the cardio-auditory syndrome of Jervell and Lange-Nielsen (recessive deafness with electrocardiographic abnormalities). J Laryngol Otol 1966: 80:451-70.

10. Friedmann I, Fraser GR, Froggatt P. Pathology of the ear in the cardio-auditory syndrome of Jervell and Lange-Nielsen. Report of a third case with an appendix on possible linkage with the Rh blood group locus. J Laryngol Otol 1968; 82:883-96.

11. Nomura Y, Mori W. Hypophosphatasia. Histopathology of human temporal bones. J Laryngol Otol 1968; 82:1129-36.

12. Naunton RF, Lindsay JR. Concretions in the stria vascularis. Arch Otolaryngol 1973; 97:376-80.

13. Bergstrom L-V, Thompson P, Sando I, Wood RP II. Renal disease, its pathology, treatment and effects on the ear. Arch Otolaryngol 1980; 106:567-72.

14. Bergstrom L-V, Jenkins P, Sando I, English GM. Hearing loss in renal disease: clinical and pathological studies. Ann Otol Rhinol Laryngol 1973; 82:555-74.

15. Oda M, Preciado MC, Quick CA, Paparella MM. Labyrinthine pathology of chronic renal failure patients treated with hemodialysis and kidney transplantation. Laryngoscope 1974; 84:1489-506.

16. Nadol JB. Electron microscopic observations in a case of long-standing profound sensorineural deafness. Ann Otol Rhinol Laryngol 1977: 86:507-17.

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AUDITORY BRAINSTEM RESPONSES IN CHILDREN WITH EARLY RECURRENT MIDDLE EAR DISEASE

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Auditory brainstem responses were recorded from an experimental group of 15 children with early histories of recurrent middle ear disease for the purpose of examining the effects of reduced auditory input on auditory brainstem function. The responses from these children were analyzed in terms of absolute latencies, interwave latencies and latency shifts across sensation level. Comparisons were made to a control group of children with no history of middle ear disease. Results indicated significant differences between the groups. The experimental group demonstrated greater absolute latencies for waves III and V as well as greater interwave latencies. These findings support the interpretation of an association between early recurrent middle ear disease and brainstem function.

INTRODUCTION

In the developing human and nonhuman organism, the immature auditory nervous system reflects predictable alterations in both the latency and waveform of evoked potential activity, suggesting the occurrence of a significant maturation period.[1-3] The plasticity observed during this time frame may make the development of an organism's neural pathway susceptible to changes in auditory input. There is considerable support for this position in the animal literature.[4-6] Additionally, studies involving human subjects have shown histologic evidence of neural degeneration in both children and adults following years of sensorineural deficit.[4,7,8] Alterations in behavioral responses, which suggest retrocochlear involvement, have been observed in persons with experimental and pathological conductive losses.[9,10] The results of these studies suggest the possibility that, under certain circumstances, reduced auditory input may have an effect on neural development and behavioral performance.

The animal literature in both visual and aural domains suggests that neural systems tend to be plastic only during critical periods of development. Little or no physiologic change has been found when mature animals are subjected to the same experimental conditions.[5,6,11,12] Although the human literature has shown some evidence of changes in behavioral responses of adult subjects who have been auditorally deprived, the question of changes in neural physiology following a reduction of input to a developing yet functioning auditory system has not been addressed. This may be the result of the inavailability of direct yet noninvasive measures of neural functioning in humans. A comparatively recent tool in use today, however, the auditory brainstem response (ABR) has been shown to provide valuable insights in the assessment of neural pathway integrity.

The ABR is a brief latency, multiphasic electrophysiologic response that is felt to reflect the electrical activity arising from a subset of neurons within the eighth auditory nerve and brainstem structures.[13] This response can be recorded noninvasively from the scalp and is capable of reflecting both peripheral and central functioning in the auditory system.

The use of the ABR as a measure of central nervous system status has been described by numerous authors in the areas of maturation and aging,[2,14-16] diagnosis of lesions along the auditory pathway,[17] and in the diagnosis of nonspecific neurological disease.[18,19] The latency values between waves I and V of the ABR have been used to assess neural differences between groups. Decreased neural capabilities are reflected in increased wave I-to-V intervals when compared to the normative values.[17]

Reports from auditory deprivation research have shown that nuclei in the brainstem are susceptible to deterioration and/or physiological modification as a result of reduced input.[4-6,20] The ABR has been selected for use because of its procedural ease and demonstrated sensitivity to disorders in this portion of the nervous system.[17-19]

It is assumed then that the fluctuating hearing levels seen in young children with early onsets of recurrent middle ear disease would have created conditions of reduced auditory stimulation. These children would serve as suitable subjects for an investigation into the effects of reduced stimulation

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From the Child Development and Mental Retardation Center, University of Washington, Seattle (Folsom, Thompson), and the Center for Speech and Hearing Disorders, Duke University Medical Center, Durham, North Carolina (Weber). This research was supported by research grants from the National Foundation-March of Dimes (grant no. 6-241) and Maternal and Child Health (grant nos. MC-R-530358-02-0 and MCT00913).

on the development of the auditory neural pathways. This study proposes that early fluctuation of hearing levels in humans, as seen in recurrent middle ear disease, may alter the development of the brainstem portion of the auditory nervous system in a fashion observable in potentials evoked from that portion of the auditory pathway.

METHODS

Subjects. Thirty children comprised the subject population for this study. These children were drawn from the research subject pool at the Child Development and Mental Retardation Center, University of Washington, Seattle, and the population at large. Inclusion in this study was based upon the following criteria:

1. All subjects were drawn from a common socioeconomic pool as determined by family income, parent education and employment status.
2. Through the use of a health status questionnaire, all subjects were screened and excluded from the study if there was a reported history of permanent hearing loss, prematurity, prenatal or perinatal trauma which might affect neural development, neurological disease or trauma, diabetes or kidney disease.
3. All subjects were 6 to 10 years old. All children functioned at grade level in school and did not exhibit mental retardation or obvious behavioral/emotional disorders.

Experimental Group. This group consisted of 15 children (ten girls, five boys) who ranged in age from 6 years 4 months to 10 years 11 months (mean = 7 years 11 months). In addition to the selection criteria for participation in this study, inclusion in this group was based upon multiple recurrent bouts of otitis media with fluid (minimum of six bouts) with the initial bout occurring at or prior to 12 months of age. Confirmation of this history was established by, in most cases, direct reports from the child's pediatrician or otolaryngologist and, in all cases, parent interviews. An attempt was made to select children with a severe history of middle ear disease. Some had received myringotomies with tubes. All had been described by physicians and/or parents to have had "long episodes" or "continually recurring otitis media." It should be noted that these children had not received hearing evaluations at regular intervals throughout the period of recurrent middle ear disease. Consequently, the precise degree of hearing impairment cannot be documented in each child for each bout of ear infection. Nonetheless, it has been shown that recurrent otitis media is nearly always accompanied by a mild-to-moderate (20 to 45 dB) conductive hearing loss by the very nature of the presence of middle ear fluid.[21-24] Accordingly, it can be assumed that children who have suffered recurrent middle ear disease throughout early childhood would also have experienced fluctuating hearing impairment during that time.

Tympanometry was performed on each subject. Two experimental subjects had pressure-equalization tubes in place at the time of testing which were deemed patent by tympanometric results. The remaining experimental subjects had tympanometric results in the normal range.

Control Group. The control group consisted of 15 children (nine girls, six boys) who ranged in age from 6 years 6 months to 10 years (mean = 8 years 1 month). None of these children had histories of hearing loss, earache, impacted cerumen, middle ear drainage or middle ear disease. Confirmation of this was established by, in some cases, direct reports from the child's pediatrician as well as, in all cases, parent interviews. In addition to the selection criteria for participation in this study, inclusion in the control group also required that normal tympanograms be obtained at the time of the ABR data collection.

Protocol. The amplified DC logic output of an electronic timer, set to a duration of 0.1 ms, was delivered to a TDH-39 headphone to generate an acoustic rarefaction click. Thresholds for the click stimuli were established for each subject allowing stimuli to be presented in decibel sensation level (SL) with regard to that individual's own threshold.

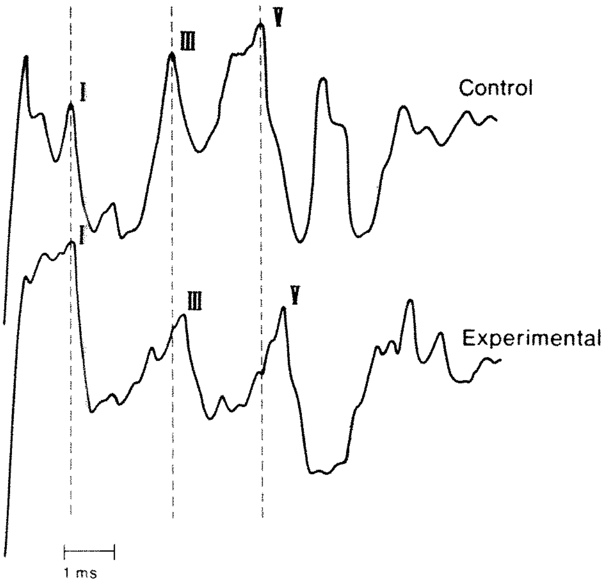

Fig 1. ABR results from two selected subjects representing each group. Latency values for these subjects approximate respective group means. Vertical dotted lines represent positions of waves I, III and V in control subject. (Intensity = 70 dB SL; rate = 13.3/s; 1,024 sweeps).

Electroencephalic activity was picked up by gold-plated EEG electrodes attached to the midline of the forehead (active) and the ipsilateral mastoid (reference). The contralateral mastoid served as the site for the ground electrode. The impedance of the electrodes was maintained at $< 5{,}000\ \Omega$. The response was amplified 10^6 times and passed in a frequency band between 100 and 3,000 Hz (3-dB down points). This bioelectric activity was then fed to a signal averager set to scan a 10-ms epoch. The final averaged response was the result of 1,024 stimulus presentations.

After the procedures had been fully explained to the child and his/her parent(s) and informed consent was obtained, the EEG electrodes were attached. Subjects were tested in a sound-treated room while reclining on a cot. The TDH-39 headphones were held in a standard headband and were placed over both ears. The child's behavioral hearing threshold for the click stimulus was then obtained in each ear, as the ears were assessed individually.

Subjects were encouraged to relax and sleep, if possible. Test clicks were initiated and, after a 3-second delay to reduce any muscle artifact that may accompany stimulus onset, the signal averager was activated. Stimulus repetition rate was fixed at 13.3/s to establish the wave I, III and V intervals and at 33.3/s to establish the latency/intensity functions. The latency/intensity functions were developed utilizing the intensity levels of 30-, 50- and 70- dB SL. All tracings were written out on an X-Y plotter.

Stimulus intensity conditions were presented in a quasi-randomized order for each ear. A control run for each ear was inserted along with the stimulus conditions to aid in the assessment of the ABR scoring reliability. Each ear was assessed with the initial ear assigned in a counterbalanced fashion.

Tympanograms were obtained on a Grason-Stadler 1722 middle ear analyzer. For this study, a normal tympanometric result was defined as a compliance peak between two and ten arbitrary compliance units that occurred within the pressure range of + 50 to − 100 mm H_2O.

Data Analysis. Auditory brainstem response tracings were scored by measuring the distance in centimeters from stimulus onset to the peak of waves I, III or V. Following each test session, tracings were scored independently by two judges who were blind to the category to which each subject belonged (ie, control or experimental). The latency values for each ear were averaged for that subject for a total number of 15 subjects for each group.

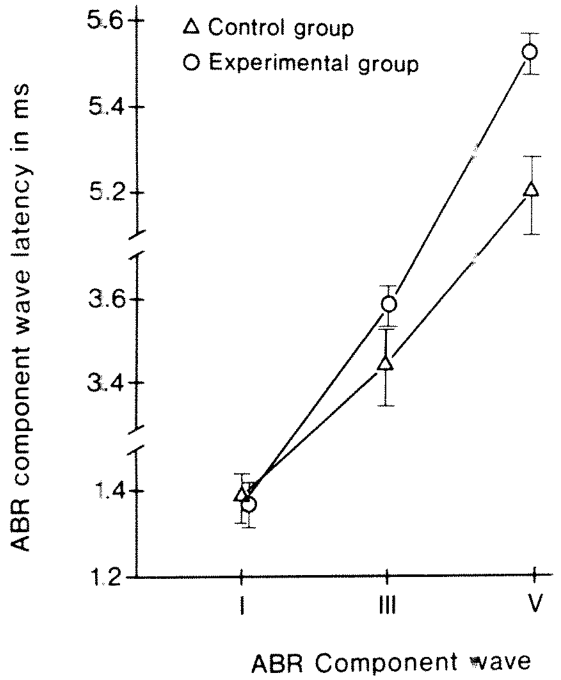

Fig 2. Mean ABR component wave latencies for control and experimental groups. Click stimuli were presented at 70 dB SL with click rate held constant at 13.3/s. Vertical bars represent ± twice standard error of mean (N = 15).

Differences between groups and among conditions were tested for significance using a repeated measures analysis of variance design. Simple main effects were assessed when a significant group-by-wave or group-by-intensity interaction was found. Interwave latencies and latency shifts for each intensity change were compared between groups using *t* tests.

RESULTS

Figure 1 shows an example of ABR responses recorded from two subjects representing the experimental and control groups. The subjects' tracings were selected so as to reflect typical waveforms and latencies for their respective groups. Wave I latencies are virtually identical while differences exist for waves III and V, with the experimental subject showing the longer latencies.

Figure 2 shows mean ABR component wave latencies for the control and experimental groups when the auditory stimulus was held constant at 70-dB SL. The graph shows a progressive divergence of the two groups when moving from the lower to more rostral brainstem levels as represented by waves I through V.

TABLE 1. RESULTS OF COMPARISONS BETWEEN CONTROL AND EXPERIMENTAL GROUPS FOR MEAN LATENCY VALUES

	ABR Waves (ms)		
	I	*III*	*V*
Control group (N = 15)	1.39 (.09)	3.45 (.08)	5.21 (.10)
Experimental group (N = 15)	1.38 (.10)	3.57 (.19)	5.54 (.17)
F values	.04	6.82	47.16

Standard deviations shown in parentheses.

Results were examined for statistical significance using a two-factor analysis of variance design. There were differences between the groups (F = 15.6, p < .01) and, as expected, across ABR component waves (F = 11995.6, p < .01). In addition, there was a significant interaction between groups and waves (F = 21.3, p < .01). The significant interaction implies that differences between groups were not uniform across the component waves. In order to test for group differences at each specific wave, simple main-effect comparisons were made. These results are shown in Table 1. There is no difference between groups for wave I (F = .04, NS) but significant differences are seen between groups for wave III (F = 6.82, p < .05) and for wave V (F = 47.16, p < .01).

The divergent nature of the group differences was tested by making group comparisons for waves I-to-III and III-to-V intervals. Results are shown in Table 2. While the overall latency interval is smaller for waves III-to-V (1.76 and 1.97) compared to waves I-to-III (2.06 and 2.19), the magnitude of group differences is greater in the III-to-V interval (.21) than in the I-to-III interval (.13). Group differences were significant for both the wave I-to-III and the wave III-to-V intervals (*t* = 2.53, p < .05; *t* = 4.67, p < .01). These findings support the interpretation of progressive brainstem differences between groups.

Figure 3 shows wave V latency differences between groups as a function of SL. Results indicate a consistent pattern of group differences regardless of stimulus SL. Longer latencies can be observed for the experimental group at 30-dB SL (F = 15.07, p < .01) and 50-dB SL (F = 61.25, p < .01) in addition to 70-dB SL (F = 21.07, p < .01).

DISCUSSION

The results of this study support the interpretation of an association between early recurrent middle ear disease and brainstem function. Repeated episodes of transient hearing loss during early developmental years may be an etiologic factor in this association. The absence of wave I differences and the presence of wave V differences between groups is a finding that supports the contention of brain-

TABLE 2. RESULTS OF MEAN INTERWAVE LATENCY COMPARISONS BETWEEN CONTROL AND EXPERIMENTAL GROUPS

	ABR Wave Intervals (ms)	
	I-III	*III-V*
Control group (N = 15)	2.06 (.12)	1.76 (.11)
Experimental group (N = 15)	2.19 (.17)	1.97 (.13)
t values	2.53	4.67

Standard deviations shown in parentheses.

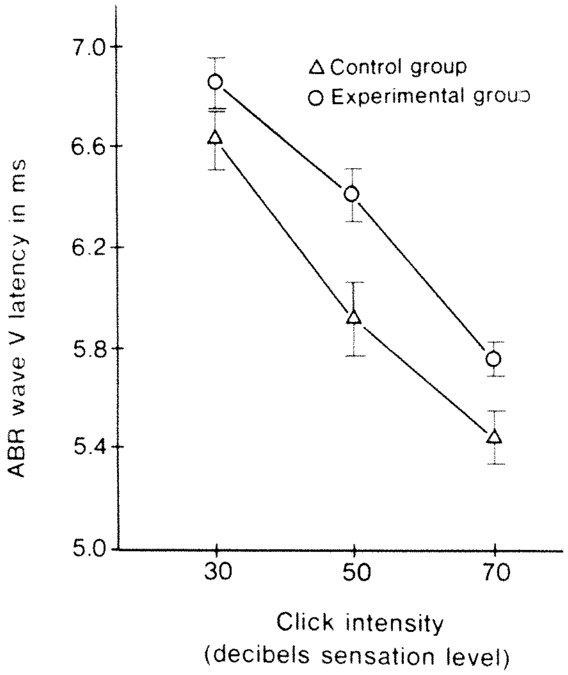

Fig 3. Mean ABR wave V latencies for control and experimental groups as a function of sensation level. Click rate was held constant at 33.3/s. Vertical bars represent ± twice standard error of mean (N = 15).

stem (as opposed to peripheral) auditory pathway abnormality.[17] The divergent nature of these group differences from ABR waves I-to-III-to-V may be consistent with either a generalized reduction in numbers of neural fibers[4] or a reflection of plasticity brought on by lack of experience at the level of the synapse.[25] The occurrence of either phenomena or the simultaneous occurrence of both would cause an overall slowing of the evoked potential latencies as observed in the experimental group.

The interpretation of a central effect in the experimental group cannot be made without consideration of other coexisting pathologies which could account for the observed increase in wave I to V intervals in this group. Among the factors which must be considered are: residual middle ear disease, the degree to which this middle ear disease may have affected cochlear function, the possibility of some underlying neural differences between groups, and the onset time of middle ear disease.

Residual Middle Ear Anomaly. The existence of recurrent middle ear disease in each subject comprising the experimental group raises the question of residual middle ear anomaly in these subjects which may have contributed to the ABR latency differences. In fact, the observation of a central effect, based on wave V latencies alone, could create a false-positive interpretation in the presence of undetected middle ear anomalies.

The results obtained in this study do not support the existence of residual anomaly in the experimental group as a contributing factor to the observed latency differences for the following reason. Though absolute latencies of waves I and V can be prolonged by middle ear problems which create conductive hearing loss, a more accurate differentiation of a central from a peripheral effect is found when utilizing the ABR wave I-to-V interval. This interwave latency value is felt to be insensitive to the presence of middle ear disorders as long as equal sensation levels are preserved during testing[26] as in this study. Also, consideration of residual middle ear disease can be minimized because of no systematic difference between groups for behavioral click thresholds or tympanometric results.

Alterations in Cochlear Function. There also exists the possibility that recurrent middle ear disease in the experimental group had in some fashion invaded or caused damage to the cochlea in some or all of the children in the experimental group. The possibility may exist not only in the chance of an invasion of the cochlear duct by viral or bacterial infection but also through some unknown effect of transient hearing deficit on hair cell function during early developmental years. The results of this study, however, do not support the existence of cochlear involvement in the experimental group as a result of or in conjunction with early middle ear disease. As noted above, subjects (control and experimental) did not differ on the basis of stimulus threshold. Further, the latency/intensity functions obtained across sensation levels of 30, 50 and 70 dB do not converge at the high intensities and are, in fact, nearly parallel (Fig 3), suggesting that cochlear involvement was not a factor in the experimental group. Finally, the ABR wave I-to-V intervals are felt to be insensitive to cochlear hearing losses, except for some slight decreases in wave I-to-V intervals in patients with severe, abruptly sloping high-frequency hearing losses.[27] The divergent relationship of the control and experimental groups, as shown in Figure 2, would not support the existence of a significant cochlear contingent in the experimental group in that the wave I-to-V interval is actually longer in this group.

Underlying Neural Differences. A screening procedure helped to insure that none of the subjects had a history of seizures, neurologic disease, neuromuscular disease, prematurity, diabetes, or kidney disease. It is felt that the control and experimental groups did not differ on the basis of these items. However, the scope of this study did not incorporate either a functional or alternate physiological component which would assure that subtle undetected neural differences did not exist on some systematic basis between the control and experimental groups. Thus, it is possible that the relationship between ABR latencies and early middle ear disease is dependent on a variable unexamined in this study.

None of the children in the study were retarded nor did they function as learning-disabled children. Therefore, it was not expected that any of the children in the experimental group would have latency values that would cause them to be considered pathological. Both the control and the experimental groups fell within the range of values encompassing ± 2 SD from the mean of our laboratory norms for wave I-to-V interval. Although they fell into this range, the groups could be differentiated on the basis of their ABR latency values.

Onset of Middle Ear Disease. Time of onset of middle ear problems was controlled in this study in that all subjects in the experimental group had onsets (first bout of middle ear effusion) prior to 12 months of age. Examination of variations in onset time, therefore, is not possible. An additional question which should be posed in a subsequent study is whether the time of onset is a variable to be considered in investigations into central differences between groups with early history of middle ear disease. This variable has been found to be of considerable importance in auditory plasticity studies using lower animals.[4-6,20] Exploration of this question warrants further study.

CONCLUSIONS

This study used ABR to investigate auditory pathway function in children with early recurrent middle ear disease. The data were compared to a control group of children with no history of middle ear involvement.

Results indicated differences between groups for the ABR waves III and V latency values, waves I-to-V intervals and wave V latency/intensity functions. These results suggest that early middle ear disease, with its accompanying fluctuations in hearing levels, may contribute to long-term central effects which persist after bouts of middle ear disease have been medically reversed.

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REFERENCES

1. Jewett D, Romano M. Neonatal development of auditory system potentials averaged from the scalp of rat and cat. Brain Res 1972; 36:101-15.

2. Hecox K. Electrophysiological correlates of human auditory development. In: Cohen L, Salapatek P, eds. Infant perception: from sensation to cognition. Vol II. Perception of space, speech and sound. New York: Academic Press, 1975:151-91.

3. Salamy A, McKean C. Postnatal development of human brainstem potentials during the first year of life. Electroencephalogr Clin Neurophysiol 1976; 40:418-26.

4. Webster D, Webster M. Neonatal sound deprivation affects brainstem auditory nuclei. Arch Otolaryngol 1977; 103: 392-6.

5. Clopton B, Silverman M. Plasticity of binaural interaction. II. Critical period and changes in midline response. J Neurophysiol 1977; 40:1275-80.

6. Clopton B, Silverman M. Changes in latency and duration of neural responding following developmental auditory deprivation. Exp Brain Res 1978; 32:39-47.

7. Lawrence M, Johnsson L. The role of the organ of Corti in auditory nerve stimulation. Ann Otol Rhinol Laryngol 1973; 82: 464-72.

8. Otte J, Schuknecht H, Kerr A. Ganglion cell populations in normal and pathological human cochleae — implications for cochlear implantation. Laryngoscope 1978; 88:1231-46.

9. Katz J. The effects of conductive hearing loss on auditory function. ASHA 1978; 209:879-86.

10. Florentine M. Relation between lateralization and loudness in asymmetrical hearing losses. J Am Aud Soc 1976; 1: 243-51.

11. Wiesel T, Hubel D. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. J Neurophysiol 1965; 28:1029-40.

12. Barlow H. Visual experience and cortical development. Nature 1975; 258:199-204.

13. Achor J, Starr A. Auditory brain stem responses in the cat. I. Intracranial and extracranial recordings. Electroencephalogr Clin Neurophysiol 1980; 48:154-73.

14. Hecox K, Galambos R. Brainstem auditory evoked responses in human infants and adults. Arch Otolaryngol 1974; 99:30-3.

15. Fujikawa S, Weber B. Effects of increased stimulus repetition rate on brainstem electric response (BER) audiometry as a function of age. J Am Aud Soc 1977; 3:147-50.

16. Rowe M. Normal variability of the brain-stem auditory evoked response in young and old subjects. Electroencephalogr Clin Neurophysiol 1978; 44:459-70.

17. Coats A. Human auditory nerve action potentials and brainstem evoked responses: latency-intensity functions in detection of cochlear and retrocochlear abnormality. Arch Otolaryngol 1978; 104:709-17.

18. Shah S, Bhargava V, Johnson R, McKean C. Latency changes in brainstem auditory evoked potentials associated with impaired myelination. Exp Neurol 1978; 58:111-8.

19. Parving A, Elberling C, Smith T. Auditory electrophysiology: findings in multiple sclerosis. Audiology 1981; 20:123-42.

20. Silverman M, Clopton B. Plasticity of binaural interaction. I. Effect of early auditory deprivation. J Neurophysiol 1977; 40: 1266-74.

21. Olmstead R, Alvarez M, Moroney J, Eversden M. The pattern of hearing following acute otitis media. J Pediatr 1964; 65:252-5.

22. Reed D, Struve S, Maynard J. Otitis media and hearing deficiency among Eskimo children. A cohort study. Am J Pub Health 1967; 57:157-62.

23. Harrison R, Phillips B. Observations on hearing levels of preschool cleft-palate children. J Speech Hear Dis 1971; 36:252-6.

24. Nozza R. Detection of pure tones in quiet and noise by infants and adults. [Unpublished doctoral dissertation.] University of Washington, 1981.

25. Greenough W, West R, DeVoogd T. Subsynaptic plate perforations: changes with age and experience in the rat. Science 1978; 202:1096-8.

26. Stockard JE, Stockard JJ, Westmorland B, Corfits J. Brainstem auditory-evoked responses. Normal variation as a function of stimulus and subject characteristics. Arch Neurol (Chicago) 1979; 36:823-31.

27. Coats A, Martin J. Human auditory nerve action potentials and brain stem evoked responses: effects of audiogram shape and lesion location. Arch Otolaryngol 1977; 103:602-22.

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FROZEN-SECTION AUTORADIOGRAPHY OF THE COCHLEA: EVIDENCE FOR DIFFERENTIAL DISTRIBUTION OF AMINO ACIDS

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A histological method is described for embedding the whole cochlea in an egg yolk medium that permits frozen sectioning in the midmodiolar plane. Resulting tissues can be processed using standard autoradiographic techniques and stained with Nissl or silver impregnation methods. Following identical intracochlear injections of tritiated proline or leucine and frozen sectioning of embedded cochleae, differential uptake patterns within the cochlea were revealed for these amino acids. Frozen sectioning of the cochlea promises to provide an efficient means to examine specific labeling patterns within the cochlear duct for compounds suspected of contributing to cochlear function by permitting the application of multiple histological techniques including routine stains and anterograde and retrograde tracers.

INTRODUCTION

A number of recent studies have established the usefulness of autoradiographic techniques to investigate various aspects of cochlear function including afferent connections to the central nervous system. For example, following intracochlear injections of tritiated amino acids,[1-7] the cochlear nucleus (CN) is labeled in a manner consistent with the afferent innervation patterns described by classic terminal degeneration methods.[8-11] In addition, the detailed incorporation patterns of transported radioactivity around specific CN cell-types appear to be related to the arrangements of synaptic input to these cells previously determined by more traditional techniques.[2-7] The use of autoradiographic tracing methods has also demonstrated that separate, labeled amino acids can be incorporated at different sites within the cochlea[12] or transported from the cochlea to the CN in a preferential manner.[8]

The results described below indicate that studies employing tracer substances to describe the central projections of primary eighth nerve fibers should be interpreted with caution unless information concerning the uptake and distribution of labeled compounds by peripheral structures is available. Autoradiographs of cochleae obtained from plastic- or paraffin-embedded tissues following perilymphatic injection of tritiated amino acids in normal animals have shown that within the cochlea, label is widely incorporated into primary afferent dendrites and fibers and their spiral ganglion somas.[1,6] However, to our knowledge, no one has shown that two common amino acids are consistently distributed in a differential manner within the cochlea following identical injection procedures.

MATERIALS AND METHODS

Preliminary studies using intracochlear injections of tritiated proline in four subjects consistently showed complete labeling, while two identically injected leucine animals demonstrated evidence for only partial distribution of the amino acid marker. To further study these observations, within-subject comparisons of both cochlear and brainstem distribution patterns were made in eight leucine- and two proline-injected guinea pigs, ranging in weight from 250 to 350 g. As an additional control, one of the proline subjects was injected with leucine on the opposite side.

Prior to intracochlear injections of [^{3}H]leucine ([^{3}H]leu, New England Nuclear, NET-460, specific activity > 110 Ci/mmol) or [^{3}H]proline ([^{3}H]pro, Amersham, TRK-439, specific activity 65 Ci/mmol), all guinea pigs were anesthetized with a mixture of ketamine hydrochloride (Vetalar, 30 mg/kg) and xylazine (Rompun, 5 mg/kg). The left round window membrane was surgically exposed, opened, and perilymph removed by means of an absorbent dental pledget. Using a microsyringe, an injection of 5 μl containing 10 μCi/μl of [^{3}H]leu or [^{3}H]pro dissolved in sterile physiological saline was made into the scala tympani. The round window fenestra was then sealed by applying a layer of Durelon dental cement. After a 24- or 48-hour survival period, animals were deeply anesthetized with sodium pentobarbital (Nembutal) and perfused intracardially with neutral-buffered formalin (10% formaldehyde buffered with sodium phosphate, 0.02 *M*). Immediately after removal of the brain, each temporal bone was dissected out, the bulla trimmed to completely expose the cochlea, and the round and oval windows opened to allow fixative to infiltrate by immersion. All tissues remained in fixative at room temperature for two weeks prior to further processing.

At the end of this period, brains were placed in 30% formol sucrose (30 g sucrose/100 ml neutral-buffered formalin) until sinking, prepared for frozen sectioning, and cut in the transverse plane at 30 μm. Resulting tissues were mounted, air-dried, and processed for standard light microscopic autoradiography using a four-week-exposure period and Kodak NTB-2 emulsion, D-19 developer, and undiluted Rapid Fix.[13] Developed sections were stained with 1% neutral red and coverslipped for subsequent bright- and darkfield microscopic analysis.

Following formalin fixation, cochleae were decalcified using a 10% Versene regimen. First, specimens were rinsed in two changes of double-distilled water and placed in uncapped vials containing 10% Versene for three days at 37°C. Next, the Versene solution was adjusted to room temperature and changed every five days until decalcification was complete, typically requiring 10 to 12 weeks. After decalcification, over a two-day period, the Versene was diluted to 5% with double-distilled

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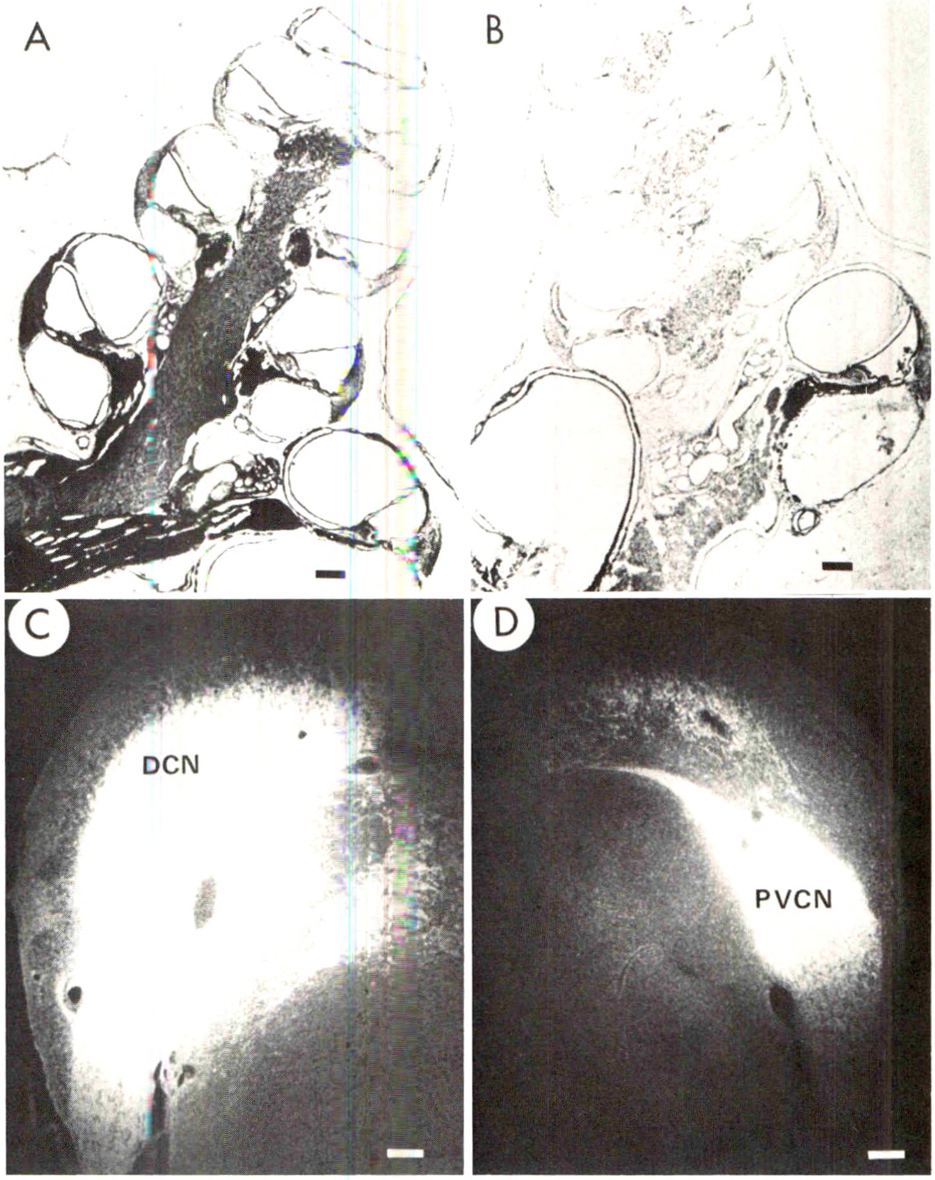

Fig 1. A,B) Low-power photomicrographs of autoradiographs of midmodiolar frozen sections through the cochlea following intracochlear injection of 50 μCi A) [^{3}H]proline or B) [^{3}H]leucine into the left (pro) and right (leu) cochleas of the same animal. Proline labeled almost entire cochlea while leucine was restricted to lower turns. C,D) Transverse sections of brainstem illustrating pattern of distribution of silver grains corresponding to transport of C) [^{3}H]pro and D) [^{3}H]leu to the dorsal (DCN) and posteroventral (PVCN) cochlear nuclei (CN) corresponding to injected cochleas shown above. Distributions of transported radioactivity to CN directly paralleled cochlear uptake patterns. (Bars = 200 μm)

water and then to 2.5% at 4°C, after which the tissue was set in cold double-distilled water overnight. At this point, egg yolk embedding was begun following methods previously described for brain tissue.[14,15] The egg yolk medium was prepared by vigorously stirring the yolk of one medium-sized hen's egg. The specimen was then removed from the distilled water solution and dried by gentle rotation on a clean paper towel with a fine camel-hair brush. Next, all surfaces were painted with the egg yolk mixture and the cochlea placed into a peel-away mold lightly coated with egg yolk medium. Additional egg yolk was added to just cover the specimen and the mold placed overnight in a covered Petri dish at 4°C. These procedures permitted air bubbles to escape from the egg yolk while preventing excessive adhesion of the specimen to the container or drying of the medium by evaporation.

The following day the specimen was gently removed from the mold and placed in a small, porous paper embedding boat and again covered with cold, freshly prepared egg yolk medium. The boat was wrapped with perforated (pin holes) aluminum foil to provide rigidity and floated on a solution of 25% formalin in a covered container for 24 hours to solidify the egg yolk mixture by allowing entry of formaldehyde by dialysis. The tissue block was then trimmed according to orientation indicators placed on the embedding boat, and the embedded cochlea was placed in 30% formol sucrose for 48 hours. At this point, the cochlea was sectioned at 20 μm using standard frozen-sectioning techniques and collected in 2% formalin. It has been our experience that thinner 5- to 10-μm sections can be cut from this material if so desired.

One series from each cochlea was processed for autoradiography in a manner identical to the brainstem tissues described above and these sections were stained with toluidine blue. The remaining two series were stained using several routine techniques including a slightly modified Harris's hematoxylin-eosin, Kluver and Barrera's luxol-fast blue, cresyl violet, and silver impregnation stains of Nauta and Gygax[16] and Fink and Heimer.[17]

RESULTS

Figure 1 shows autoradiographs obtained from midmodiolar cochlear sections following intrascalar 50-μCi injections of either [^{3}H]pro (Fig 1A) or [^{3}H]leu (Fig 1B), and corresponding brainstem autoradiographs (Fig 1C,D, respectively) showing transport to the dorsal (DCN) and posteroventral (PVCN) cochlear nucleus. Our most striking finding was that following identical round window injections of the [^{3}H]amino acids, differential labeling patterns within the cochlea were observed, and

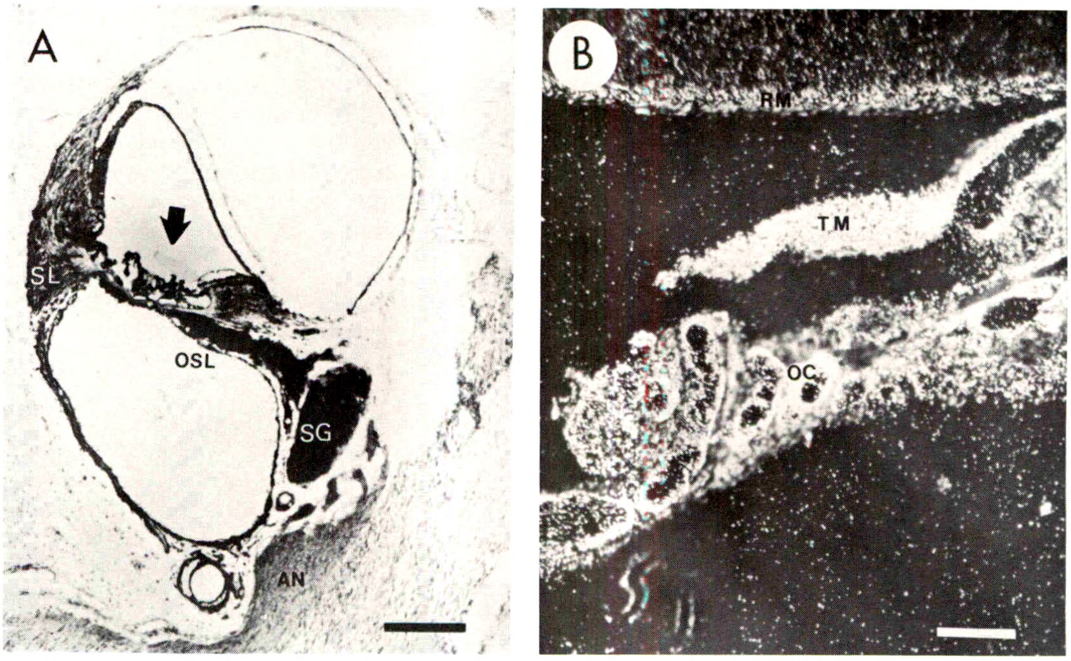

Fig 2. A) Autoradiograph of individual cochlear turn demonstrating detailed distribution pattern of [^{3}H]leu following standard injection into perilymphatic spaces. Note heavy label in spiral ligament (SL), afferent nerve fibers in osseous spiral lamina (OSL), spiral ganglion cells (SG), and emerging auditory nerve fibers (AN). Tectorial membrane located directly below arrow is lightly labeled and was often marked in this manner throughout cochlea in absence of dense label in upper turns. (Bar = 200 μm) B) Higher magnification, darkfield micrograph of organ of Corti from another section that includes region indicated by arrow in A. Note that tectorial membrane (TM) and Reissner's membrane (RM) are labeled along with entire organ of Corti (OC). Details of peripheral end-organ are essentially obscured by heavy accumulations of silver grains. (Bar = 20 μm)

these distinct incorporation patterns were maintained during transport to the CN. Thus, [^{3}H]leu (N = nine cochleae) was consistently restricted to the basal and first turns (Fig 1B), whereas an identical injection of [^{3}H]pro (N = two cochleae) was distributed much more completely throughout all cochlear turns (Fig 1A). Within the CN, consistent with the peripheral uptake pattern for [^{3}H]pro, the majority of DCN and PVCN was labeled along with eighth nerve fiber projections to the lateral vestibular nucleus (Fig 1C). Following injection of [^{3}H]leu, however, only the high-frequency regions of DCN and PVCN showed transported radioactivity (Fig 1D). Although proline was widely incorporated throughout the cochlea, an overall labeling gradient, greatest in the lower turns near the injection site and least in the apical regions, was still apparent. The results shown in Figure 1 were obtained from the right and left cochleae and brainstem of the same animal, and, for the most part, rule out individually related variations in axonal transport kinetics, tissue processing techniques, etc, that could contribute to the different incorporation patterns seen after [^{3}H]leu and [^{3}H]pro injections. It should be noted that specific activity did not appear to account for these results since [^{3}H]pro, with the lowest specific activity, was more generally incorporated.

The brightfield photomicrograph of Figure 2A shows in more detail the typical labeling pattern of the tritiated amino acids, in this case [^{3}H]leu, within a particular cochlear turn. It is clear that the afferent dendrites in the habenula, spiral ganglion cells, and emerging eighth nerve fibers were all densely labeled with silver grains as indicated by the significant accumulations of radioactive particles over these areas. In addition, the spiral ligament showed heavy uptake of the tracer compounds. The higher magnification darkfield photomicrograph of Figure 2B supports the observation that essentially all structures of the cochlear duct including the organ of Corti and tectorial membrane incorporated [^{3}H]leu. Specific details of the organ of Corti were obscured by the dense accumulation of silver grains over this region. Given the large amounts of localized radioactivity and our standard exposure times, no detailed differences in regional incorporation of [^{3}H]leu compared to [^{3}H]pro were apparent. Thus, the pattern of labeling in the CN did not appear to be the result of a preferential utilization of leucine or proline by separate morphological elements within the cochlea, but rather a difference in regional distribution.

DISCUSSION

Recent studies have relied upon axonal transport of labeled amino acids from the cochlea either to trace eighth nerve fiber connections to the central nervous system[1-5] or identify putative neurotransmitters.[6] Common to all investigations has been the intracochlear injection of various labeled compounds and the assumption that substances introduced in this manner were generally incorporated throughout the cochlea. The results of the present study, however, have direct implications for studies in which tracing techniques are used to determine functional connections. It is apparent that intrascalar injection without local cochlear perfusion can frequently result in nonuniform distributions of tracer materials, a finding that has been only cursorily addressed in a few earlier reports.[1,4,5] Such sporadic uptake following a round window-injection route poses serious problems for quantitative interpretation of axonally transported substances to the CN.

Based on evidence presented here, an even more serious consideration is the observation that [^{3}H]leu was incorporated differently within the cochlea than [^{3}H]pro, thus further complicating the interpretation of results from studies describing the transport of amino acids. In our hands, the pattern of uptake for [^{3}H]leu or [^{3}H]pro in the guinea pig was surprisingly consistent between animals, suggesting a minimal role for injection-procedure variables and implicating the type of amino acid as a major contributing factor in explaining differential incorporation. This notion is consistent with the observations demonstrated in Figure 1 which illustrate the distinctive distributions of [^{3}H]pro versus [^{3}H]leu in left and right cochleas, respectively, of the same animal.

We interpret the findings of a different pattern of utilization for the two amino acids to be of a biological origin and not related to methodological considerations since every precaution was taken to use identical injection and tissue preparation procedures. More convincing is the fact that proline readily gained access to vestibular nerve afferents, probably due to its greater propensity to cross cell membranes or, perhaps, areas of cellular specializations, ie, the "tight junctions" that surround the scala media.[18] Thus, following injections of [^{3}H]pro, not only was the vestibular nerve heavily labeled in our subjects as well as those of others,[1,7] but proline also has been reported in these same studies to be easily transported transsynaptically throughout the brainstem auditory system. Neither of the above observations readily occurs following even substantial injections of [^{3}H]leu. These results argue strongly that the two amino acids actively cross cellular barriers and participate in binding and consequent cellular transport processes, each in its own unique manner. It is noteworthy that in an earlier study performed in this laboratory, identical intracochlear injections of horseradish peroxidase (HRP) resulted, at times, in incomplete anterograde labeling of the CN,[19] with this particular tracer's central distribution pattern most resembling that of proline.

Our results with tritiated leucine showing uptake in primary dendrites, spiral ganglion cells, and eighth nerve fibers are consistent with previous in vitro[12] and in vivo experiments[1,7] demonstrating that [^{3}H]leu was uniformly incorporated by all elements of the organ of Corti, thus suggesting active transport of this material. These observations are also in agreement with a variety of reports documenting the tendency for a number of compounds to cross the basilar membrane and enter the organ of Corti.[18]

Preferential labeling of [^{3}H]leu and [^{3}H]pro is not unique to either the auditory nervous system or to sensory systems in general.[20] In a recent report describing differences in the pattern of neuronal labeling following separate injections of the two amino acids in the dorsal column nuclei of the cat, Molinari and Berkley[20] suggest a number of hypotheses to explain their observations of differential incorporation. Several of these hypotheses may also explain the similar outcome observed in the present study. Thus, documented inner ear regional differences in metabolic needs would influence the rate that basal versus apical cells synthesize particular proteins; that proline, a nonessential amino acid, plays a greater role in the transmission of neural impulses than leucine and consequently is taken up more generally by the system is also possible; differences in membrane transport characteristics or rate of uptake for proline and leucine would result in one compound having greater time to diffuse throughout the cochlea; evidence in other neural systems that glial cells actively incorporate proline implicates these cells as important intermediaries in the transsynaptic transport of this amino acid; and, finally, a damaged cochlea, perhaps due to the toxic effects of the physiological saline carrier, may stimulate an increase in synthesis for a specific protein that requires leucine as a substrate resulting in its immediate and complete uptake. Although it is at present unclear how cochlear mechanisms of amino acid utilization account for the differences in cellular incorporation patterns of [^{3}H]leu and [^{3}H]pro observed here, it is apparent that a simple round window injection of tracer does not consistently demonstrate the complete projection pattern of the cochlear division of the eighth nerve.

The findings reported in this study indicate that frozen-sectioned cochlear tissues yield autoradiographic results comparable to those obtained with standard plastic- or paraffin-embedding procedures. Most importantly, the frozen-sectioning method allows for rapid processing of histological sections and in the absence of harsh organic solvents, results in considerably less tissue shrinkage and distortion.

We have shown here convincing evidence that frozen sectioning provides an efficient means to perform autoradiography on the entire cochlea or to study specific patterns of radioactivity within the cochlea for any number of compounds suspected of being important to cochlear function. The frozen-sectioning method also will permit examination of anterogradely transported materials from damaged cochleae or, conversely, retrogradely transported substances from the CN that promise to result in important contributions to the study of a number of unresolved issues currently of concern to the auditory physiologists and anatomists. For example, the relation between the functional activity of single CN neurons and their specific cochlear loci in both normal and damaged ears could be readily determined following retrograde transport of microinjected quantities of labeled HRP from the CN to the cochlea. Once the nature of cochlear insults necessary to block normal tracer uptake is known, the injection of tracers promises to become an efficient method for surveying the status of remaining nerve fibers in the traumatized ear. Perhaps, as suggested earlier by Jones and Casseday,[3] the use of labeling techniques to indicate the location of intact hair cells corresponding to the projections of functional nerve fibers will reveal new details concerning the principle of tonotopicity in the peripheral auditory system.

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REFERENCES

1. Carpenter MB, Batton RB III, Peter P. Transport of radioactivity from primary auditory neurons beyond the cochlear nuclei. J Comp Neurol 1978; 179:517-33.

2. Jones DR, Casseday JH. Auditory nerve: projections from cochlea demonstrated by autoradiographic methods. Brain Res 1978; 148:224-9.

3. Jones DR, Casseday JH. Projections to laminae in dorsal cochlear nucleus in the tree shrew. *Tupaia glis*. Brain Res 1979; 160:131-3.

4. Jones DR, Casseday JH. Projections of the auditory nerve in the cat as seen by anterograde transport methods. Neuroscience 1979; 4:1299-313.

5. Kane ES. Autoradiographic evidence of primary projections to the caudal cochlear nucleus in cats. Am J Anat 1977; 150:641-52.

6. Kane ES. Central transport and distribution of labelled glutamic and aspartic acids to the cochlear nucleus in cats: an autoradiographic study. Neuroscience 1979; 4:729-45.

7. Kelly JP, Hudspeth AJ, Kennedy S. Transneuronal transport in the auditory system of the cat. Brain Res 1978; 158:207-12.

8. Feldman ML, Harrison JM. The projection of the acoustic nerve to the ventral cochlear nucleus of the rat. A Golgi study. J Comp Neurol 1969; 137:267-94.

9. Lewy FH, Kobrak H. The neural projections of the cochlear spirals on the primary acoustic centers. Arch Neurol Psychiat 1936; 35:839-52.

10. Lorente de No R. Anatomy of the eighth nerve. III. General plan of structure of the primary cochlear nuclei. Laryngoscope 1933:43:327-50.

11. Osen KK. Course and termination of primary afferents in the cochlear nucleus of the cat. An experimental anatomical study. Arch Ital Biol 1970; 108:21-51.

12. Gulley RL, Fex J, Wenthold RJ. Uptake of putative neurotransmitters in the organ of Corti. Acta Otolaryngol (Stockh) 1979; 88:177-82.

13. Hendrickson AE, Moe L, Noble B. Staining for autoradiography of the central nervous system. Stain Technol 1972; 47:283-90.

14. Ebbesson SOE. The selective silver-impregnation of degenerating axons and their synaptic endings in nonmammlian species. In: Nauta WJH, Ebbesson SOE, eds. Contemporary research methods in neuroanatomy. New York: Springer Verlag, 1970:132-61.

15. Snodgress AB, Dorsey CH. Egg albumin embedding: a procedure compatible with neurological staining techniques. Stain Technol 1963; 38:149-55.

16. Nauta WJH, Gygax PA. Silver impregnation of degenerating axons in the central nervous system: a modified technique. Stain Technol 1954; 29:91-3.

17. Fink RP, Heimer L. Two methods for selective silver impregnation of degenerating axons and their synaptic endings in the central nervous system. Brain Res 1967; 4:369-74.

18. Nadol JB Jr. Intercellular fluid pathways in the organ of Corti of cat and man. Ann Otol Rhinol Laryngol 1979; 88:2-11.

19. Martin GK, Lonsbury-Martin BL, Wise RP. Demonstration of anterograde labeling of primary auditory projections following intracochlear injections of horseradish peroxidase in the guinea pig. Neurosci Lett 1980; 18:113-8.

20. Molinari HH, Berkley KJ. Differences in glial and neuronal labeling following [^{3}H]proline or [^{3}H]leucine injections into the dorsal column nuclei of cats. Neuroscience 1981; 6:2313-34.

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TOPOGRAPHIC ARRANGEMENT OF MOTONEURONS INNERVATING THE SUPRAHYOID AND INFRAHYOID MUSCLES

A HORSERADISH PEROXIDASE STUDY IN CATS

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The topographic arrangement of motoneurons innervating the muscles which participate in the rostrocaudal movement of the larynx was studied in cats by means of the horseradish peroxidase (HRP) method. After HRP injection into these muscles, all labeled neurons were found in the nuclei of the brainstem and cervical nerves (C1, C2) ipsilaterally. The mylohyoid and anterior digastric motoneurons were seen in a cluster in the medial part of the rostrocaudal area of the motor trigeminal nucleus. Within the medial part of the nucleus, the mylohyoid motoneurons were located ventrally and the anterior digastric motoneurons dorsally. The posterior digastric neurons were situated in the accessory facial nucleus, the stylohyoid neurons in the ventral aspect of the facial nucleus, the geniohyoid motoneurons in the ventral aspect of the hypoglossal nucleus, and the thyrohyoid motoneurons in the lateral aspect of the hypoglossal nucleus and the dorsomedial part of the ventral horn cells of C1. The HRP-labeled neurons of the sternohyoid and sternothyroid muscles were observed in the central portion of the ventral horn cells of C1 and C2.

INTRODUCTION

The movement of the larynx in the rostrocaudal direction is achieved by the suprahyoid and infrahyoid muscles. During the pharyngeal stage of swallowing, the anterorostral excursion of the larynx is a most important movement as is the closure of the larynx. This laryngeal elevation is achieved mainly by the geniohyoid (GH) and thyrohyoid (TH) muscles. In addition, the mylohyoid (MH), anterior digastric (ADG) and stylohyoid (STH) muscles play a supplementary role in this laryngeal elevation.[1] On the other hand, the downward movement from the maximum elevation of the larynx is accomplished by the recoiling force and gravity. During this movement the sternohyoid (SH) and sternothyroid (ST) muscles occasionally show weak discharges on electromyograms.[2] The location of motoneurons supplying the MH and ADG muscles was investigated by Willems (in rabbits),[3] Szentágothai (in cats),[4] Vedral and Matzke (in cats)[5] utilizing the retrograde cell reaction, by Mizuno et al (in cats),[6] and Batini et al (in cats)[7] with the use of the horseradish peroxidase (HRP) method. The localization of the posterior digastric (PDG) motoneurons was investigated by Szentágothai (in cats)[8] using a Gross-Bielschowsky method in which the secondary degeneration of end-plates and motor fibers was analyzed after destroying the facial nucleus, and by Mizuno et al by means of the HRP method.[6] The STH motoneurons of cats were studied by Szentágothai[8] by means of the same technique as described above. Parhon and Goldstein (in dogs),[9] Kosaka and Jagita (in dogs),[10] and Barnard (in dogs)[11] and Stuurman (in mice)[12] reported the location of the GH and TH motoneurons investigated by means of the retrograde degeneration method. Berkelbach (in *Erinaceus europaeus*),[13] investigating serial sections of the brainstem, and Uemura et al,[14] using the HRP method, investigated the GH, TH, SH, and ST motoneurons. In 1981 we demonstrated the location of the motoneurons of the GH and the TH muscle in cats using the HRP method.[15] In all the previous studies on the localization of motoneurons innervating the suprahyoid and the infrahyoid muscles which participate in the rostrocaudal movement of the larynx, only a few selected muscles were investigated. However, there have been some conflicting opinions. The main purpose of the present study was to determine spatial relationships of the motoneurons of all the suprahyoid and infrahyoid muscles using the same technique in the same animal species. We adopted the HRP method. This study is one in a series of our studies[15-18] of the topographic arrangement of muscles related to the function of the larynx.

MATERIAL AND METHOD

Seventy cats weighing from 400 to 2,700 g were studied as follows: the MH, ADG, PDG, and STH each in ten cats, and the SH and ST each in 15 cats. There is no omohyoid muscle in cats.

The animals were anesthetized with ketamine (30 to 40 mg/kg im). After exposing the muscle, 1 to 3 μL of 30% HRP (Toyobo

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ARRANGEMENT OF MOTONEURONS INNERVATING MUSCLES WHICH PARTICIPATE IN ROSTROCAUDAL MOVEMENT OF LARYNX

Movement of Larynx	*Muscles**	*Arrangement of HRP-Labeled Neurons* *Nucleus*	 *Location in Nucleus*
Anterorostal direction	Suprahyoid		
	MH	Motor trigeminal nucleus	Ventromedial, caudal 2/3
	ADG	Motor trigeminal nucleus	Dorsomedial, caudal 2/3
	PDG	Accessory facial nucleus	
	STH	Facial nucleus	Ventral, central 3/5
	GH	Hypoglossal nucleus	Ventral, central 2/3
	Infrahyoid		
	TH	Hypoglossal nucleus	Lateral, caudal 1/3
		Ventral horn cells of C1	Dorsomedial, whole extent
Caudal direction	SH	Ventral horn cells of C1 & C2	Central, whole extent
	ST	Ventral horn cells of C1 & C2	Central, whole extent

*Innervation was ipsilateral in all cases.

grade I-C) dissolved in sterile 0.9% saline was injected manually into the muscle belly with a 10 μL microsyringe under an operating microscope. After a survival time of 24 to 48 hours, the brains of the animals were fixed by transcardial perfusion. Frozen sections through the medulla oblongata and the cervical cord were made serially at 60 μm thickness for demonstration of the enzyme; a horizontal section was done for one cat, a sagittal section for one cat, and transverse sections were done for the remaining cats in each group. Details pertaining to the procedures of HRP injection, perfusion, tissue fixation, staining and mounting have been described elsewhere.[16] The neutral red is adopted as the counterstaining in this study.

RESULTS

We have investigated the GH and TH motoneurons and reported the results elsewhere.[15] In order to relate the location of these motoneurons to that of the motoneurons of the muscles investigated in the present study, the outline of the results of the previous investigation will be described in this section.

The Table summarizes the arrangement of labeled neurons after HRP injection of the suprahyoid and the infrahyoid muscles. All of the labeled motoneurons for these muscles were found ipsilaterally. In order to facilitate understanding the results of localization of motoneurons in the suprahyoid and the infrahyoid muscles of cats, three groups of figures are presented. Figure 1 schematically shows the outline of the location of the labeled motoneurons of the muscles investigated in the horizontal and the sagittal planes of the medulla oblongata and the cervical cord. Figure 2 schematically depicts the location of the HRP-labeled motoneurons in the transverse plane of the medulla oblongata and the cervical cord at seven levels (A-G) which are indicated in Figure 1. Figure 3 demonstrates photomicrographs of nine selected sections of the brainstem and the cervical cord.

Mylohyoid Muscle and Anterior Digastric Muscle. Following HRP injection into the MH and ADG, labeled neurons were identified in the medial part of the motor trigeminal nucleus exclusively. Within this medial part of the nucleus, MH motoneurons were slightly scattered and occupied the ventral portion, while the ADG motoneurons aggregated in the dorsal portion (Figs 2A and 3A). In the horizontal plane, the motoneurons of MH and ADG were

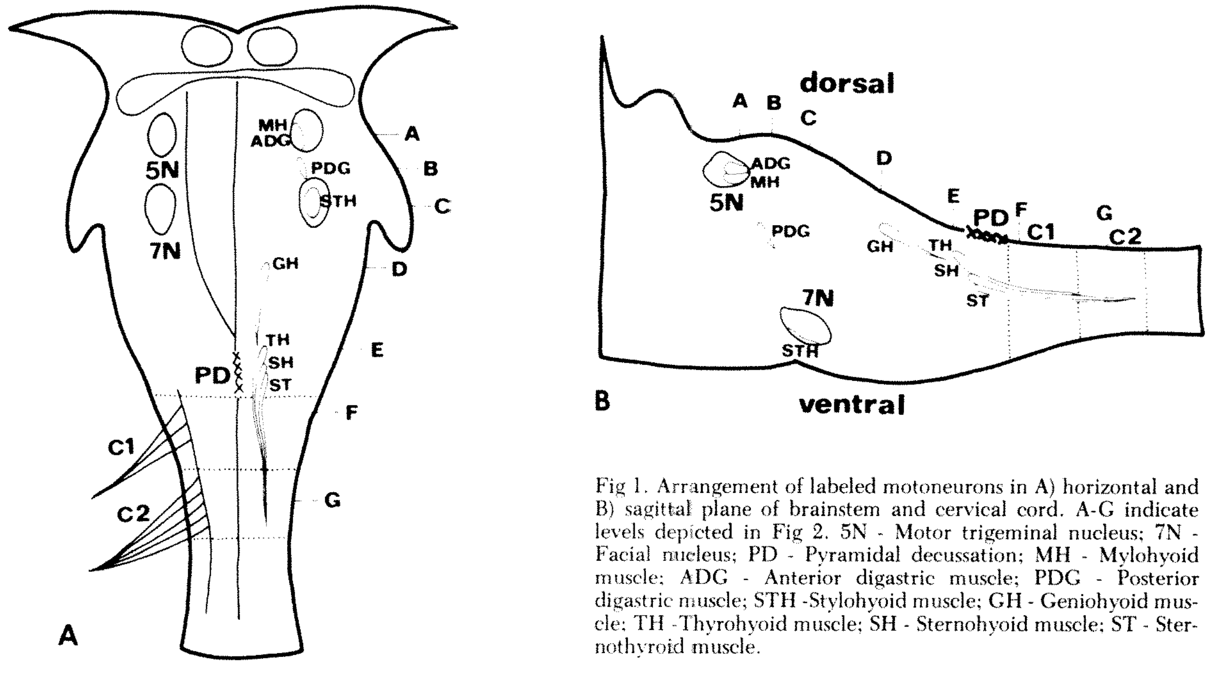

Fig 1. Arrangement of labeled motoneurons in A) horizontal and B) sagittal plane of brainstem and cervical cord. A-G indicate levels depicted in Fig 2. 5N - Motor trigeminal nucleus; 7N - Facial nucleus; PD - Pyramidal decussation; MH - Mylohyoid muscle; ADG - Anterior digastric muscle; PDG - Posterior digastric muscle; STH -Stylohyoid muscle; GH - Geniohyoid muscle; TH -Thyrohyoid muscle; SH - Sternohyoid muscle; ST - Sternothyroid muscle.

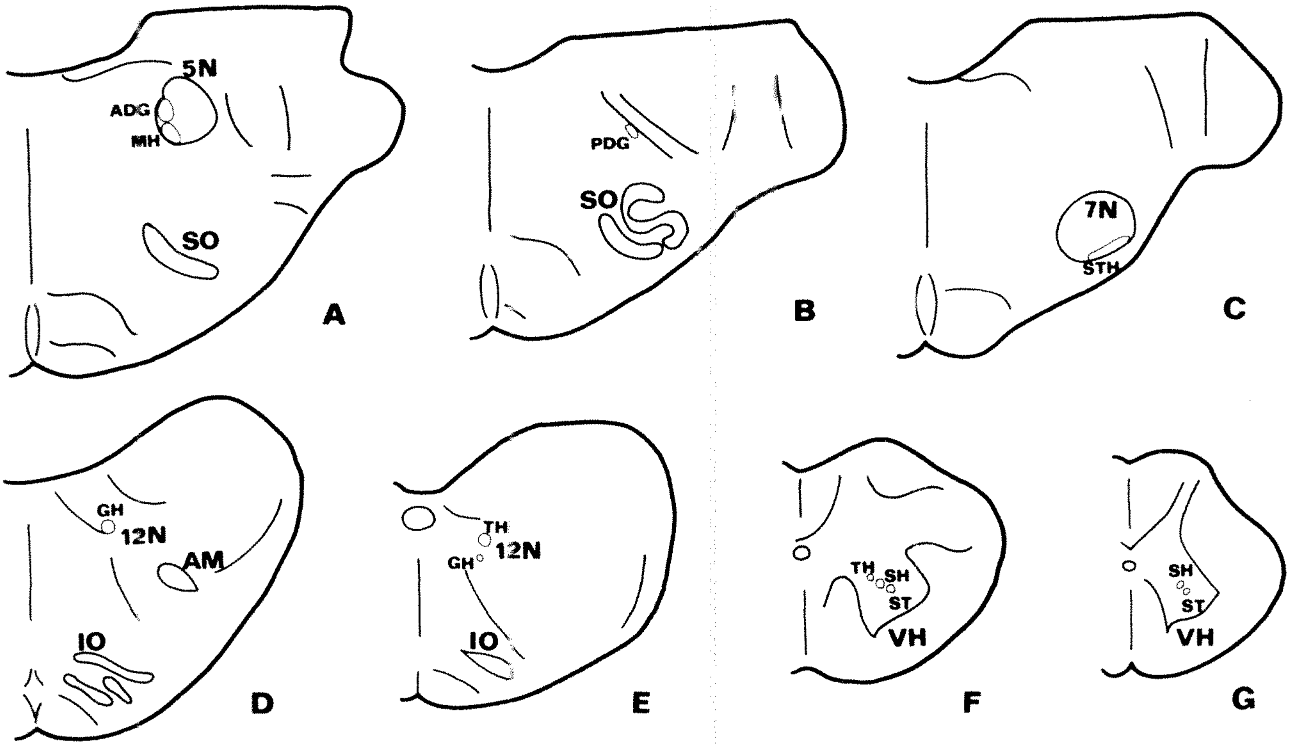

Fig 2. Transverse sections of brainstem and cervical cord showing labeled neurons of each muscle. A) Motor trigeminal nucleus; B) Between caudal part of motor trigerminal nucleus and rostral part of facial nucleus; C) Caudal part of facial nucleus; D) Caudal part of principal nucleus of inferior olive; E) Beginning of central canal; F) Rostral part of C1; G) Middle part of C2. SO - Superior olivary nucleus; 12N - Hypoglossal nucleus; AM - Nucleus ambiguus; IO - Inferior olivary nucleus; VH - Ventral horn. Muscle abbreviations as in Fig 1.

located in the caudal two thirds of the nucleus and were seen to partly overlap each other (Fig 1).

Posterior Digastric Muscle. The HRP-labeled neurons of PDG were recognized in the accessory facial nucleus (Figs 2B and 3B). This nucleus is situated in the caudal part of the motor trigeminal nucleus and is dorsorostral to the facial nucleus (Fig 1).

Stylohyoid Muscle. The neurons labeled with HRP of STH were situated in the facial nucleus. Within the facial nucleus STH motoneurons were localized ventrally in the central aspect of the nucleus (Figs 1, 2C and 3B).

Geniohyoid Muscle. The labeled motoneurons of GH were observed in the rostral two thirds of the ventral aspect of the hypoglossal nucleus (Figs 2D, E and 3C). The labeled-cell column for GH extended from the level of the well-developed portion of the principal nucleus of the inferior olivary nucleus to the level where the central canal begins (Fig 1).

Thyrohyoid Muscle. The motoneurons of TH were located in the caudal one third and lateral portion of the hypoglossal nucleus and also in the dorsomedial part of the ventral horn cells of cervical nerve (C)1 (Figs 2E, F and 3C). They extended from the level where the central canal begins to the level of the caudal part of the ventral horn of C1. The rostral end of the cell column for TH was located near the caudal end of the cell column for GH (Fig 1).

Sternohyoid Muscle and Sternothyroid Muscle. The HRP-labeled neurons of SH and ST were found in the central portion of the ventral horn cells of C1 and C2, with the SH neurons located dorsomedial to the ST neurons (Figs 2F, G and 3D). The labeled cell column for SH and ST stretched from the level of the rostral end of the pyramidal decussation to the caudal end of C2. The level of the rostral end of the labeled cell column for SH was more rostral than that of the labeled cell column for ST (Fig 1).

DISCUSSION

According to Willems,[3] Mizuno et al[6] and Batini et al[7] the motoneurons of MH and ADG in rabbits and cats were located in the ventromedial part of the motor trigeminal nucleus. In addition, Mizuno et al showed that, within the ventromedial division of the motor trigeminal nucleus, MH was represented in the ventrolateral subdivision and ADG in the dorsomedial subdivision. This location of MH and ADG motoneurons, however, is not in accordance with that reported by Szentágothai[4] and Vedral and Matzke.[5] Szentágothai showed that MH and ADG motoneurons in the cat were localized in the dorsal aspect of the motor trigeminal nucleus; Vedral and Matzke reported that the MH and ADG neurons were represented in the posterior half of the same nucleus. In these respects, our findings agree

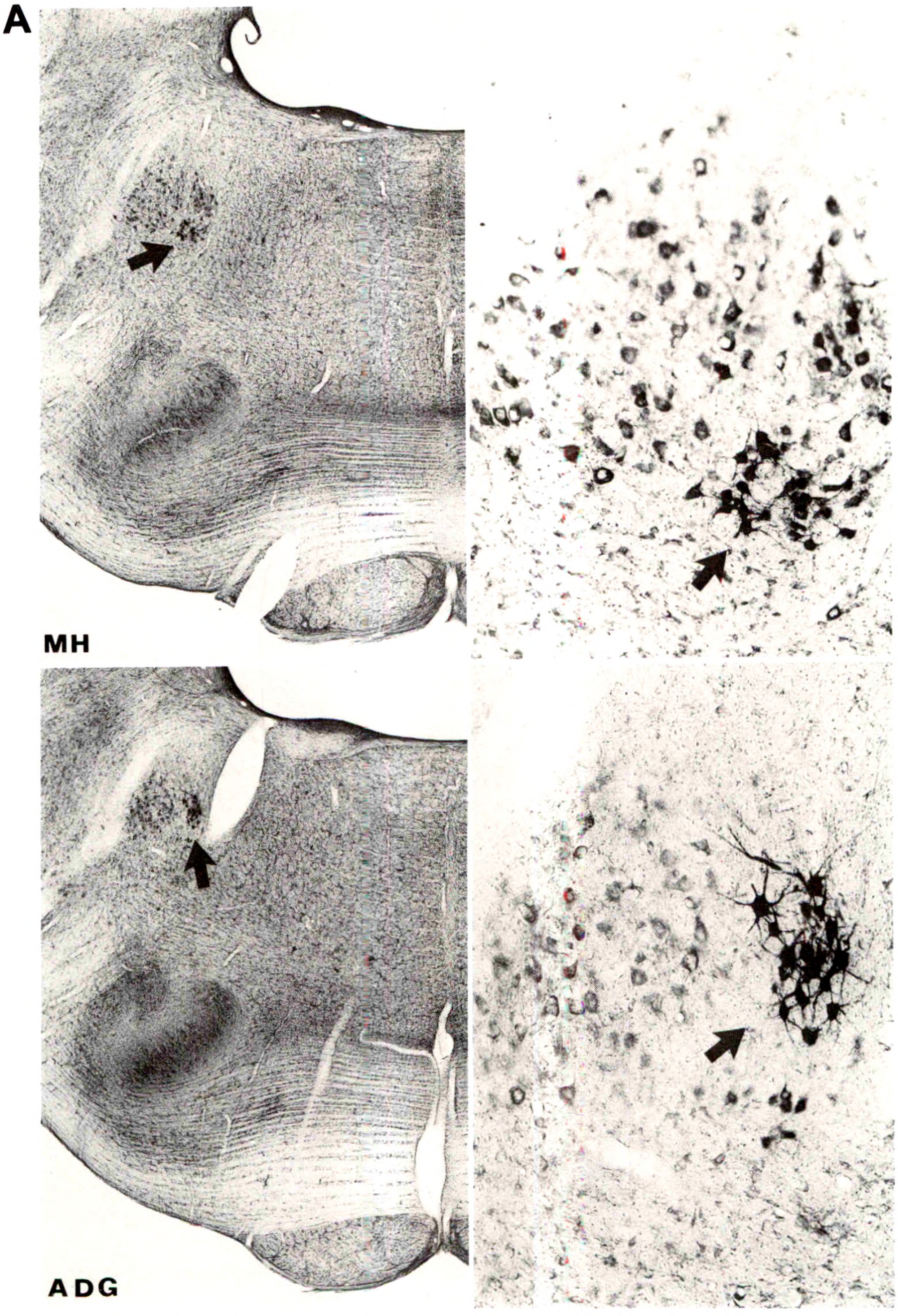

Fig 3. Cross sections of brainstem and cervical cord innervated by HRP-labeled neurons (arrows). A) MH - Mylohyoid muscle; ADG - Anterior digastric muscle. (Left - x10; right - x50)

with those of Willems, Mizuno et al and Batini. In the present investigation, the motoneurons of MH and ADG were aggregated into a cluster within the motor trigeminal nucleus and were found always in the caudal two thirds of the nucleus.

Szentágothai[8] reported and Mizuno[6] later confirmed that the efferent neurons for PDG lie outside of the facial nucleus, probably in the accessory nucleus which lies between the facial and abducent nuclei. This small group of motoneurons corresponds to the nucleus nervi facialis accessories of Taber[19] or the retrotrigeminal nucleus of Berman.[20] Our results are in general agreement with the findings of Szentágothai and Mizuno et al. In all three studies PDG motoneurons were observed in the accessory facial nucleus.

The present study also confirmed Szentágothai's data on the location of the efferent neurons of STH.

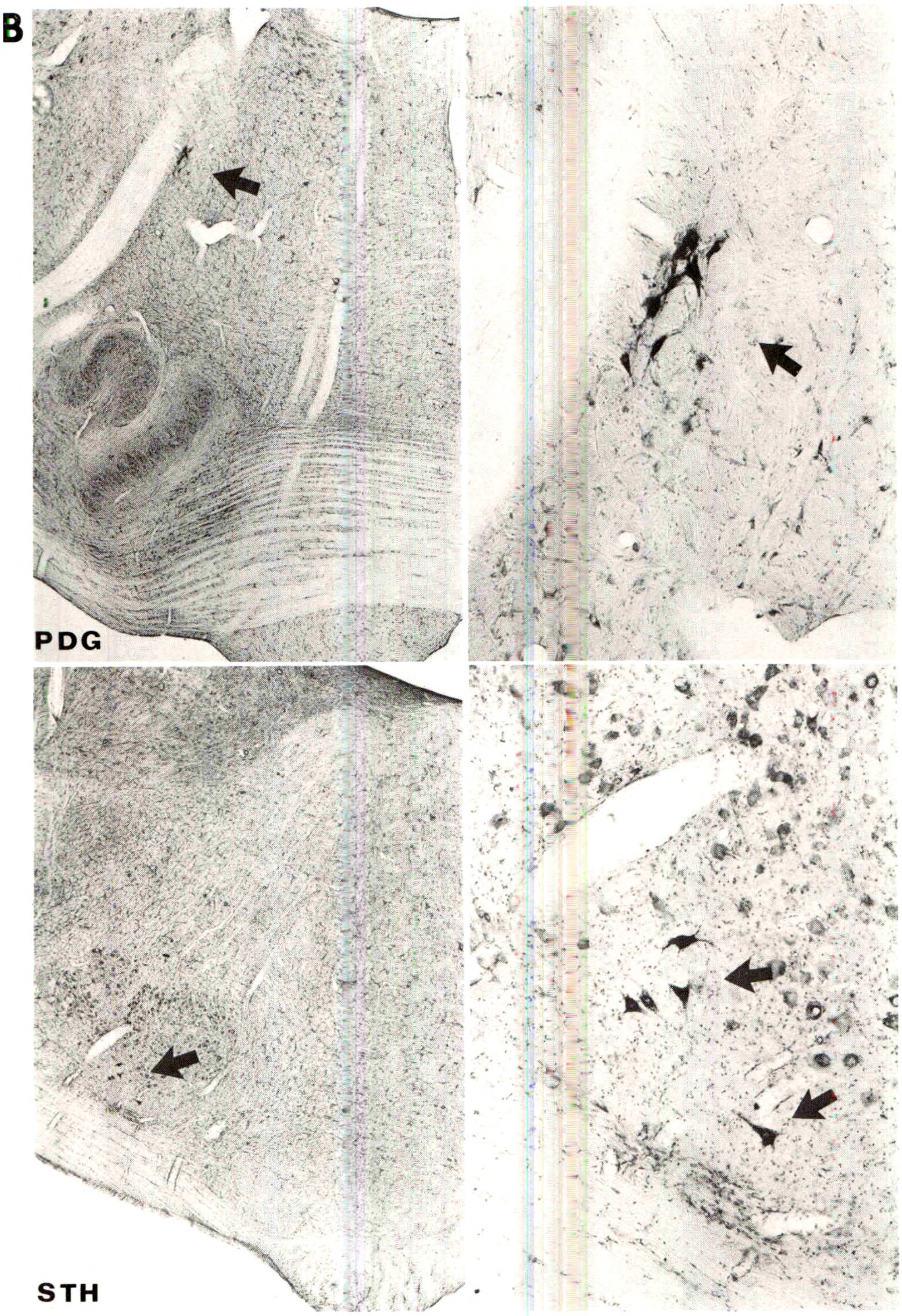

Fig 3, cont'd. B) PDG - Posterior digastric muscle; STH - Stylohyoid muscle. (Left - x10; right - x50)

Both studies identified the efferent neurons which supply STH in the posterior part of the facial nucleus dorsally and medially. Additionally, we also recognized STH motoneurons in the central aspect of the facial nucleus ventrally in all the ten animals investigated.

According to the literature, neurologists have three different opinions concerning the innervation to GH and TH. Textbooks of anatomy and otolaryngology state that the innervation is by the hypoglossal nerve, by C1 and C2, or by both of them. These theoretical differences may be explained by reviewing a description of the anatomical structure. The superior radix of the ansa cervicalis, which involves both the anterior branches of C1 and C2, partly joins with the hypoglossal nerve. The nerves which enter GH and TH branch out of the hypoglossal nerve peripheral to this union. It is not clear if some nerve fibers from C1 and/or C2 enter the hypoglossal nerve to innervate GH and/or TH. Ac-

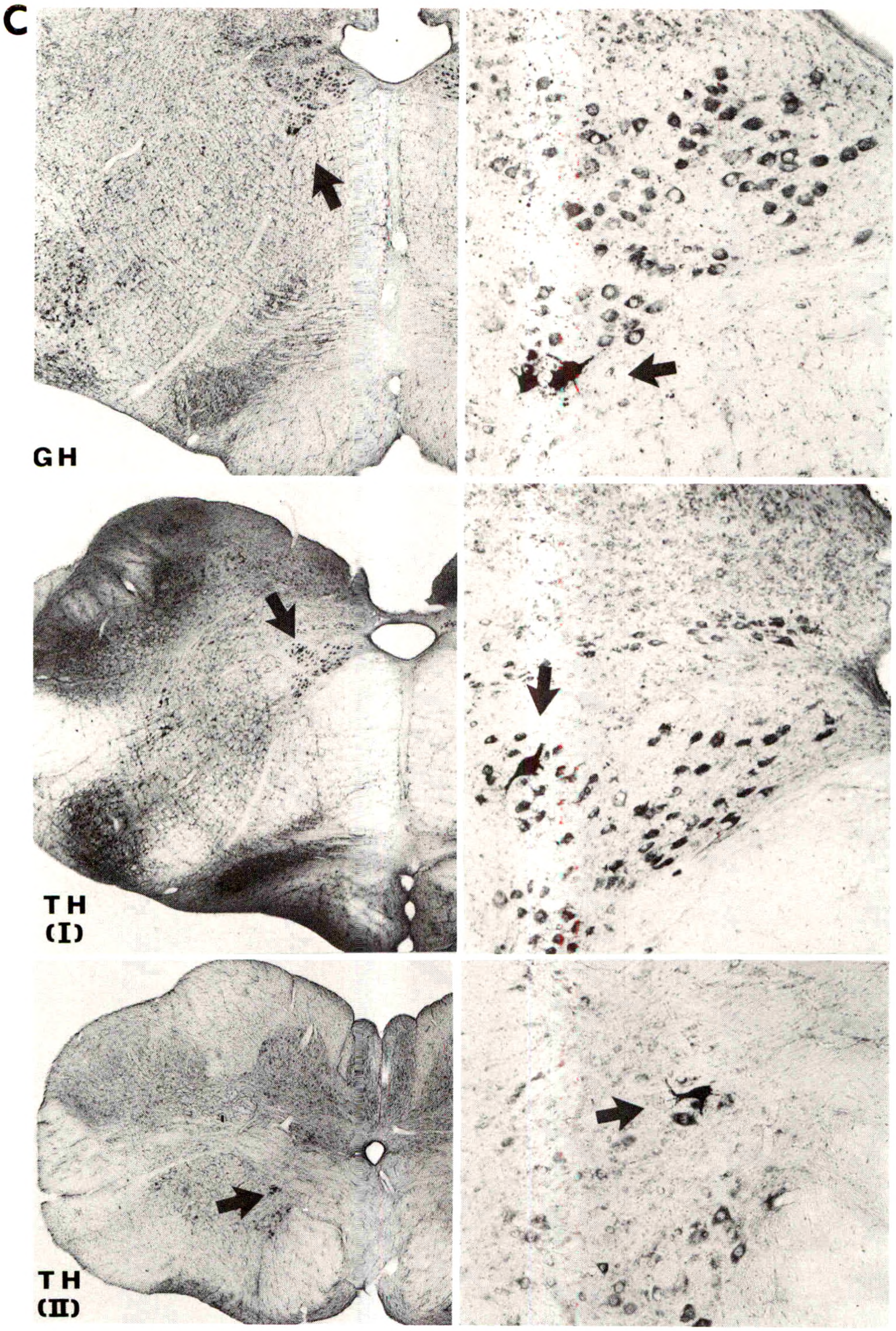

Fig 3, cont'd. C) GH - Geniohyoid muscle; TH - Thyrohyoid muscle. TH (I) is at level of caudal part of hypoglossal nucleus; TH (II) is at level of middle part of C1. (Left - x10; right - x50)

cording to Parhon and Goldstein,[9] Kosaka and Jagita,[10] and Barnhard,[11] after sectioning the descending branch of the hypoglossal nerve, retrograde cell reactions were observed in the dorsolateral part of the caudal hypoglossal nucleus. In contrast, Stuurman[12] found cell reactions in the ventral horn of the cervical cord.

Other investigators have observed that GH motoneurons were located in the hypoglossal nucleus and TH motoneurons in the C1 and C2,[13] and that the motoneurons of the GH were situated in the ventromedial division of the hypoglossal nucleus, but no labeled neurons were found within the hypoglossal nucleus after HRP injection into TH, SH and ST.[14] In the present study, the location of GH motoneurons was identified only in the ventral division of the hypoglossal nucleus, which is in agree-

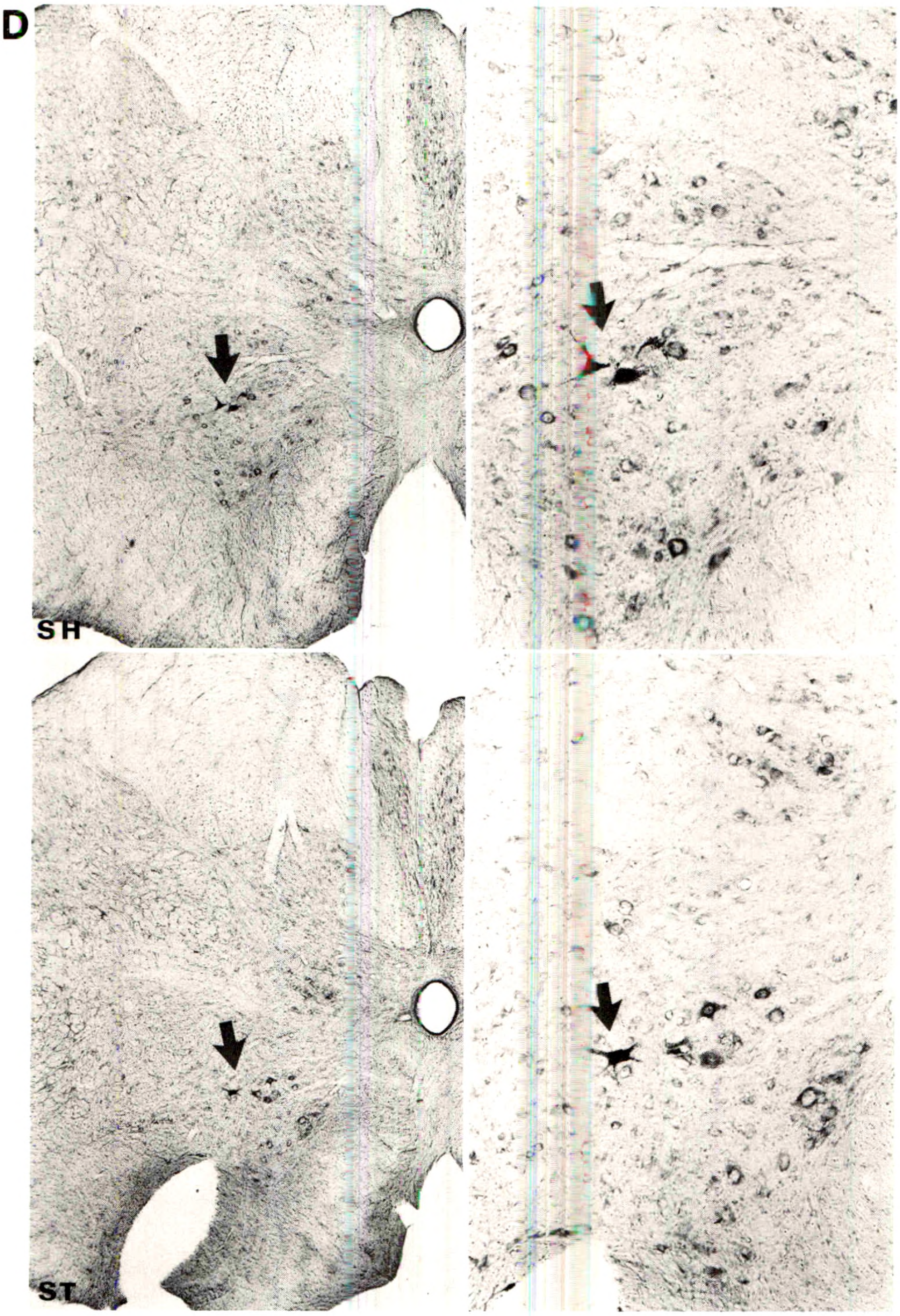

Fig 3, cont'd. D) SH - Sternohyoid muscle; ST - Sternothyroid muscle. (Left - x20; right - x50)

ment with reports of Parhon and Goldstein,[9] Kosaka and Jagita,[10] Barnhard,[11] Berkelbach,[13] Uemura et al,[14] the textbooks of Kaneko,[21] Sobotta and Figge,[22] Kopfsch,[23] McNab Jones,[24] and Williams.[25]

On the other hand, the localization of TH motoneurons was recognized both in the caudal part of the hypoglossal nucleus and in the ventral horn of C1 which support the anatomy studies of Gray[26] and Cunningham.[27]

With respect to the localization of the SH and ST motoneurons, Berkelbach[13] observed that both of them were found in the C2. According to Stuurman,[12] TH is innervated by the cervical cord and SH by C1 exclusively. As mentioned earlier, Uemura[14] reported that no labeled neurons for SH and ST were seen in the hypoglossal nucleus. By means of the HRP method, the present study demonstrated the precise location of the motoneurons of these muscles to be in the central portion of the ventral horn cells of C1 and C2.

We believe that our previous reports[15-18] and the present data on the motoneurons supplying the muscles that partake in the laryngeal function may be useful in interpreting the neurons' physiological mechanism on the control of laryngeal functions.

In summary, after HRP injection into the muscles which participate in the rostrocaudal movement of the larynges of 70 cats, all of the motoneurons with labeled peroxidase were found in the ipsilateral side. The labeled neurons of MH and ADG were recognized in the medial part of the motor trigeminal nucleus. Within this medial part of the nucleus, MH motoneurons were located ventrally and ADG motoneurons dorsally. The motoneurons of PDG were situated in the accessory facial nucleus, STH neurons of PDG were situated in the accessory facial nucleus, STH neurons in the central part of the facial nucleus ventrally, GH motoneurons in the ventral aspect of the hypoglossal nucleus, and TH motoneurons in the lateral aspect of the hypoglossal nucleus and the dorsomedial part of the ventral horn cells of C1. The HRP-labeled neurons of SH and ST were observed in the central portion of the ventral horn cells of C1 and C2. Clearly the location of the motoneurons in these muscles is only a first step in understanding laryngeal involvement in swallowing. Additional work is needed to determine axon connections in order that the physiology can be understood sufficiently well to apply this knowledge to functional movements of the larynx.

REFERENCES

1. Maeyama T. Experimental investigations of the function of the intrinsic and extrinsic laryngeal muscles during deglutition. Especially for elevation of the larynx. Otologia (Fukuoka) 1975; 21:787-807 (in Japanese).

2. Kunitake H. Electromyographic study of extrinsic laryngeal muscle in humans. Jpn J Otolaryngol 1971; 74 57-90 (in Japanese).

3. Willems E. Les noyaux masticateurs et mesencephaliques des trijumeaux chez le Lapin. Neuraxe 1910; 12:1-299

4. Szentágothai J. Functional representation in the motor trigeminal nucleus. J Comp Neurol 1949; 90:111-20.

5. Vedral D, Matzke H. Topographical localization of the muscles of mastication in the motor nucleus of the trigeminal nerve in the cat. J Hirnforsch 1967; 9:565-9.

6. Mizuno N, Konishi A, Sato M. Localization of masticatory motoneurons in the cat and rat by means of retrograde axonal transport of horseradish peroxidase. J Comp Neurol 1975; 164: 105-16.

7. Batini C, Buisseret-Delmas C, Corvisier J. Horseradish peroxidase localization of masticatory muscle motoneurons in cat. J Physiol (Paris) 1976; 72:301-9.

8. Szentágothai J. The representation of facial and scalp muscles in the facial nucleus. J Comp Neurol 1948; 88:207-20.

9. Parhon C, Goldstein M. Sur l'origine de la branche descendante de l'hypoglosse. Roum Med: Zitiert vor Nr. 3:1899.

10. Kosaka K. Jagita K. Experimentelle Untersuchungen über die Ursprünge des Nervus hypoglossus und seines absteigendes Astes. Jahrb Psychiat Neurol 1903; 24:150-89.

11. Barnard JW. The hypoglossal complex of vertebrates. J Comp Neurol 1940; 72:489-524.

12. Stuurman FJ. Die Lokalisation der Zungenmuskeln in Nucleus hypoglossi. Anat Anz 1916; 48:593-610.

13. Berkelbach van Sprenkel J. The hypoglossal nerve in an embryo of *Erinaceus europaeus*. J Comp Neurol 1924; 36:219-70.

14. Uemura M, Matsuda K, Kume K, Takeuchi Y, Matsushima R, Mizuno N. Topographical arrangement of hypoglossal motoneurons: an HRP study in the cat. Neurosci Lett 1979; 13:99-104.

15. Miyazaki T, Yoshida Y, Hirano M, Shin T, Kanaseki T. Central location of the motoneurons supplying the thyrohyoid and the geniohyoid muscles as demonstrated by horseradish peroxidase method. Brain Res 1981; 219:423-7.

16. Yoshida Y, Miyazaki T, Hirano M, Shin T, Totoki T, Kanaseki T. Location of motoneurons supplying the cricopharyngeal muscle in the cat studied by means of the horseradish peroxidase method. Neurosci Lett 1980; 18:1-4.

17. Yoshida Y, Miyazaki T, Hirano M, Shin T, Totoki T, Kanaseki T. Localization of efferent neurons innervating the pharyngeal constrictor muscles and the cervical esophagus muscle in the cat by means of the horseradish peroxidase method. Neurosci Lett 1981; 22:91-5.

18. Yoshida Y, Miyazaki T, Hirano M, Shin T, Kanaseki T. Arrangement of the motoneurons innervating the intrinsic laryngeal muscles of cats as demonstrated by the horseradish peroxidase. Acta Otolaryngol (Stockh) 1981 (in press).

19. Taber E. The cytoarchitecture of the brain stem of the cat. I. Brain stem nuclei of cat. J Comp Neurol 1961; 116:27-70.

20. Berman AL. The brain stem of the cat. A cytoarchitectonic atlas with stereotaxic coordinates. Madison: University of Wisconsin Press, 1968.

21. Kaneko U. Anatomy of the Japanese. Tokyo: Nanzando, 1973:377-8.

22. Sobotta J, Figge FH. Myology. Atlas of human anatomy: Munchen-Berlin-Wien: Urban & Schwarzenberg, 1974:170-1.

23. Kopsch FR. Das muskel system. In: Lehrbuch und Atlas der Anatomie des Menschen: Stuttgart: Georg Thieme Verlag, 1955:394-413.

24. McNab Jones RF. Anatomy of the mouth, pharynx and oesophagus. In: Ballantyne J, Groves J, eds. Scott-Brown's diseases of the ear, nose and throat. London: Butterworth, 1979: 263-311.

25. Williams RG. Anatomy of the mouth and pharynx. In: Maloney WH, ed. Otolaryngology (Cotes-Schenk). Maryland: Harper and Row, 1973:1-16.

26. Warwick R, Williams PL. Gray's anatomy. Edinburgh: Longman Group Ltd, 1973:507-8.

27. Sinclair DC. Muscles and fasciae. In: Romanes GJ, ed. Cunningham's textbook of anatomy. London: Oxford University Press, 1981:283-6.

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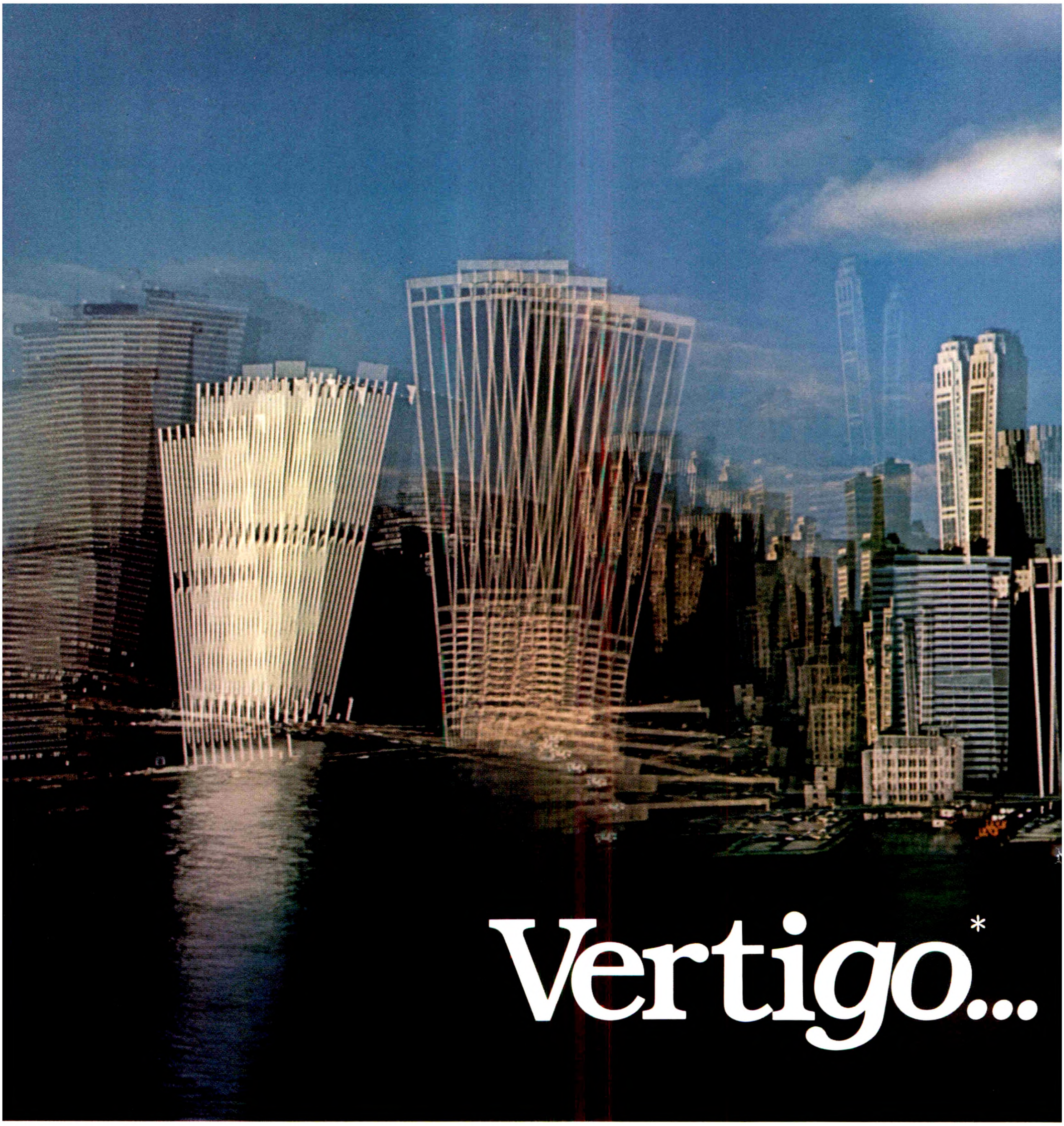

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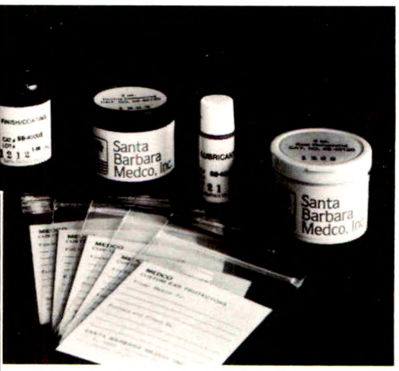

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TYPE II COLLAGEN-INDUCED AUTOIMMUNE SENSORINEURAL HEARING LOSS AND VESTIBULAR DYSFUNCTION IN RATS

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MEMPHIS, TENNESSEE

Autoimmune sensorineural hearing loss was induced in rats by immunizing them with native bovine type II collagen. Type I and denatured type II collagen, administered by an identical immunization procedure, would not induce disease. Evidence of sensorineural hearing loss was obtained by measuring the brainstem evoked potential and by observing histopathologic changes consisting of cochlear nerve degeneration and perineural vasculitis in affected animals. Immunized animals had high levels of antibodies to native type II collagen.

Deafness can be due to many different causes including infection, vascular insufficiency, drug toxicity, hereditary defects, metabolic-endocrine disorders, malnutrition, and tumors. A case report of human autoimmune sensorineural hearing loss was recently described by McCabe.[1] This new entity was established based on its clinical pattern and response to treatment. Although immunologic injury was implicated in the pathogenesis of deafness in McCabe's case report, an autoimmune etiology was not proven. If it could be shown that autoimmune mechanisms can result in hearing loss, exciting new possibilities for diagnosis and treatment of hearing disorders would be established.

In this report we describe an animal model of immunologically mediated hearing loss. Immunologic hypersensitivity to native type II collagen, a major structural component of connective tissue, has previously been shown to induce arthritis in rats[2] and mice,[3] and chondritis of the ear lobe in rats.[4] We have discovered that sensorineural hearing loss can also be induced by immunization with native type II collagen, but not with type I or denatured type II collagen. In our experiments temporal bone pathology revealed cochlear ganglion degeneration and perineural vasculitis; vestibular dysfunction was also observed. Furthermore, hearing loss was transferred by injection of a gamma globulin containing fractional amounts of sera from type II collagen-immunized animals. Our observations suggest that a definite clinical entity of deafness due to autoimmunity to type II collagen does exist.

MATERIALS AND METHODS

Female inbred Lewis rats weighing 100 to 125 g each were supplied by the Charles Rivers Company, courtesy of the National Institutes of Health. The animals were fed standard laboratory chow and water ad libitum.

Antigens used in our studies consisted of bovine and chick type II collagen and bovine type I collagen. All collagens used were extracted by limited pepsin digestion of cartilage or skin. Isolation and purification of bovine type II collagen (BII),[5] chick type II collagen,[6] and bovine type I collagen[6] were performed as previously described. The purity of the collagen preparations was determined by amino acid analysis, sodium dodecyl sulfate polyacrylamide gel electrophoresis and uronic acid analysis. In each case there was no detectable contamination by noncollagenous proteins, proteoglycans, or by other types of collagen.

Collagen for immunization was dissolved in 0.01N acetic acid by stirring overnight at 4°C. An emulsion was made by adding the collagen to an equal volume of Freund's adjuvant and homogenizing the mixture using a Virtis Homogenizer. Lewis rats received 0.1 mL of emulsion containing 100 μg of BII emulsified with incomplete Freund's adjuvant by intradermal injection into the right hind foot. The rats were boosted seven days later with an

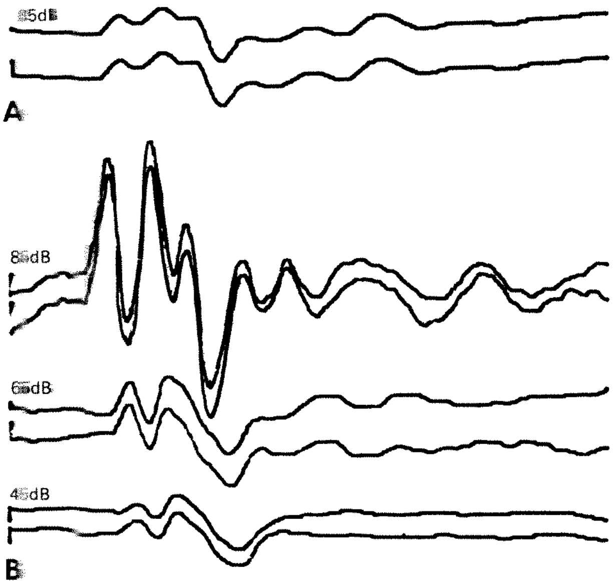

Fig 1. BSEP of rat with hearing loss. A) Stimulation at 85 dB measured as described in Methods section. No response was induced at 65 dB. Note delayed latency of peaks and low amplitude of responses. B) Control BSEP. Normal rats were stimulated at 85, 65 and 45 dB. Note differences in amplitude between these figures.

From the Department of Medicine, University of Tennessee Center for the Health Sciences and Veterans Administration Medical Center, Memphis.

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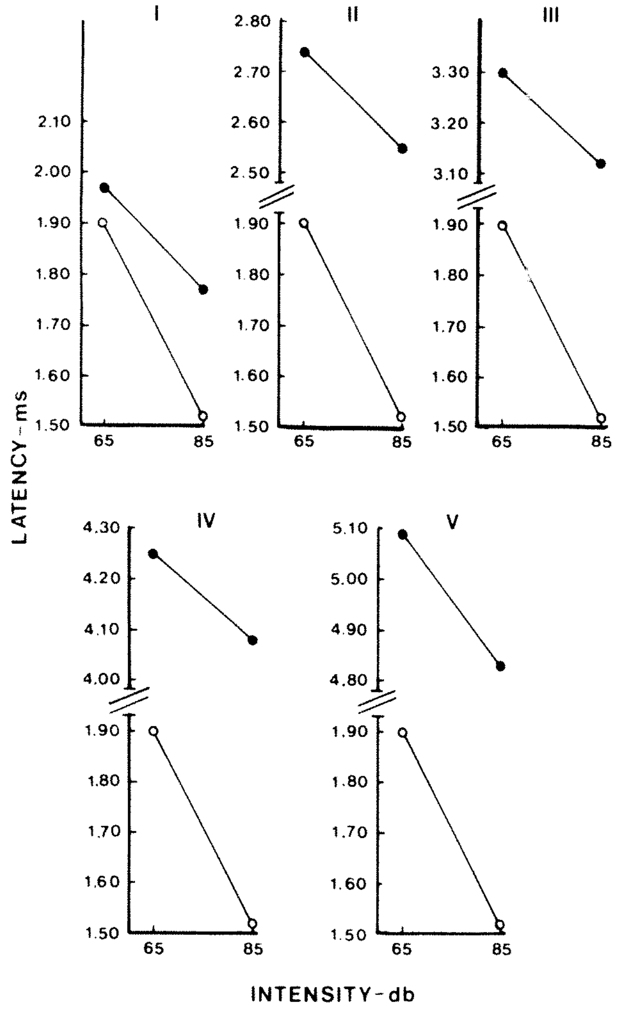

Fig 2. BSEP plotting latency *v* intensity. Immunized rats have increased latency over normal rats. ●——● - Immunized rats; ○——○ - Normal rats.

identically prepared emulsion injected intradermally into their tails. Sera for measurements of antibody were obtained two weeks after primary immunization. Animals were tested for hearing loss by brainstem evoked potential (BSEP) measurement. Immunized rats were tested at 2 weeks after primary immunization.

The potential generated in the auditory nerve and brainstem auditory pathway consists of seven positive waves occurring at specific latencies. Each peak is presumed to reflect the activity of different neural sites, with the first wave generated in the acoustic nerve.[7,8] For BSEP measurements, the animals were placed in a specially-designed testing box connected to a Nicolet CA-1000 evoked potential system.

Auditory brainstem potentials were evoked by binaural presentation of a 100-μ/s click at a rate of 15.1/s through earphones. Stimuli intensities used were 85 dB, 65 dB, 45 dB, 30 dB, and 25 dB. Monopolar recordings were taken with electrodes fixed at the vertex and the ipsilateral paw. The potentials were amplified and filtered using a band-pass of 150 Hz to 3,000 Hz. Brain electrical activity was sampled for 10 ms following the onset of a click. We measured the latencies of the first five peaks, including the interpeak latencies between peak I and each successive peak. In addition, each animal was evaluated tympanometrically, and vestibular function was tested calorically. Each ear was stimulated by infusion of 7 mL of water at 4°C. The duration of horizontal, low-amplitude, low-frequency nystagmus was then measured. It is noteworthy that BSEP and nystagmus are central manifestations from which peripheral conditions are inferred. Therefore, there are some limitations to these methods.

TABLE 1. PEAK I LATENCIES FROM BSEPs OF CONTROL AND IMMUNIZED RATS* (N = 10)

Animal/Stimuli	*85 dB* *Mean SD*	*65 dB* *Mean SD*	*45 dB* *Mean SD*
Control	1.61 ± .03	1.79 ± .05	2.16 ± .05
Experimental	1.90 ± .12	2.11 ± .14	2.38 ± .05
P	< .005	< .005	< .005

*Student's *t* test.

Sera were collected by cardiac puncture and antibody titers were assayed by an ELISA method described elsewhere.[9] In short, disposable polystyrene 96-well microtiter plates were coated with collagen dissolved in 0.4 ionic strength phosphate buffer, pH 7.6. Collagen-coated plates were incubated with phosphate buffered saline (PBS) containing 0.5% ovalbumin to block nonspecific binding. Sera, diluted at 1/1,000 with PBS containing 0.5% ovalbumin and 0.05% Tween 20, were added to the plates which were then incubated overnight at 4°C. After washing, peroxidase-conjugated goat antirat IgG was added at a predetermined dilution. After incubation at 4°C for four hours, the plates were washed three times and 100 μL of orthophenylenediamine (OPD) substrate (40 mg OPD in 100 mL phosphate/citrate buffer, pH 5.0, with 40 μL of 30% H_2O_2) was added to each well. Thirty minutes later, the colorimetric reaction was read at 490 nm by using a Dynatec MR 580 microelisa autoreader. Analysis was performed in duplicate and the results are expressed as absorbance.

After measuring BSEPs and obtaining sera for antibody determinations, the animals were killed. Their temporal bones were dissected en bloc, fixed in 95% cold ethanol and decalcified in 5% ethylenediaminetetraacetic acid buffer solution (pH 7.4). The animals were also perfused with 5% glutaraldehyde solution (pH 7.4), and their temporal bones dissected and fixed with 10% neutral buffer formalin. Decalcified tissue was immersed in 56°C paraffin, sectioned, and stained with hematoxylin and eosin by standard methods. For immunofluorescent studies, deparaffinized sections were treated with a 1:100 dilution of FITC-labeled goat antirat IgG or antirat C3 for 20 minutes, washed with PBS, and mounted with glycerin.

RESULTS

The BSEPs of control rats and immunized rats showed that amplitude and latency differed significantly. There was an absence of electrical activity in the immunized rats when they were stimulated at an intensity of 25 or 30 dB. These results indicate hearing impairment in the immunized rats (Figs 1 and 2). Table 1 shows the results of testing BSEPs in ten experimental and control rats. Amplitude was decreased, and the positive waves which occur at a specific latency were delayed. These data suggest decreased activity of different neuronal sites beginning with the first wave generated by the acoustic nerves. The shift in the latency of the first peak and the low amplitude of the response are evidence of increased neural transmission time, due to ineffective reception of physiological stimuli, and confirm the presence of sensorineural hearing loss in immunized rats. Analogous results were obtained using mice immunized with native chick type II collagen. As an additional control, rats were also immunized with bovine native type I and denatured type II collagen. Only rats or mice immunized with native type II collagen had significantly impaired hearing.

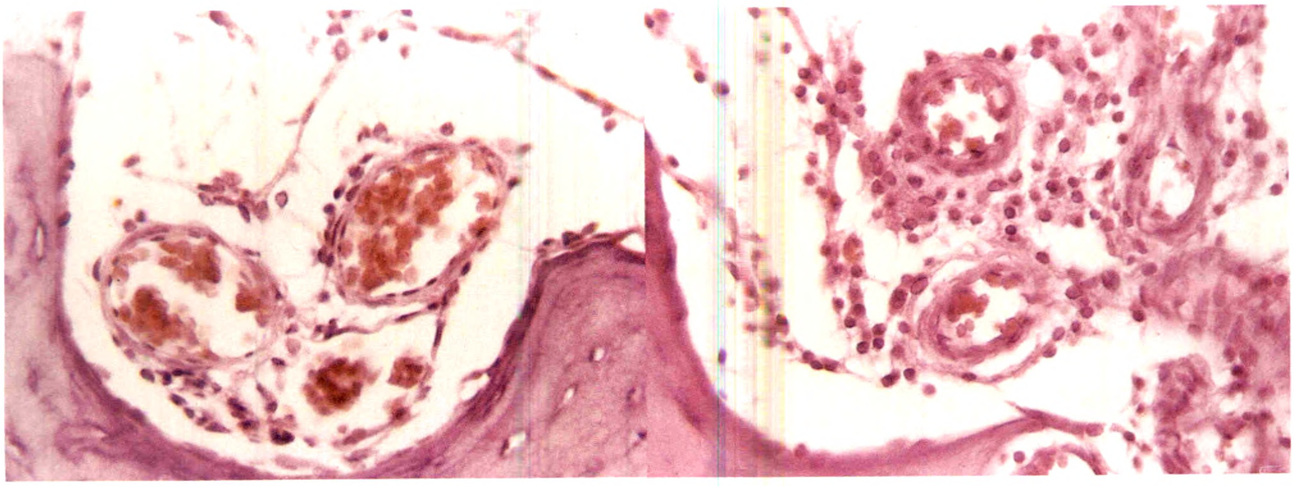

Fig 3. A) Cochlear arteries and veins from normal rat. B) Inflamed cochlear artery in autoimmune sensorineural hearing loss in rat. Vessel walls are thickened and fibrotic. (H&E, x240; micrograph x3,840)

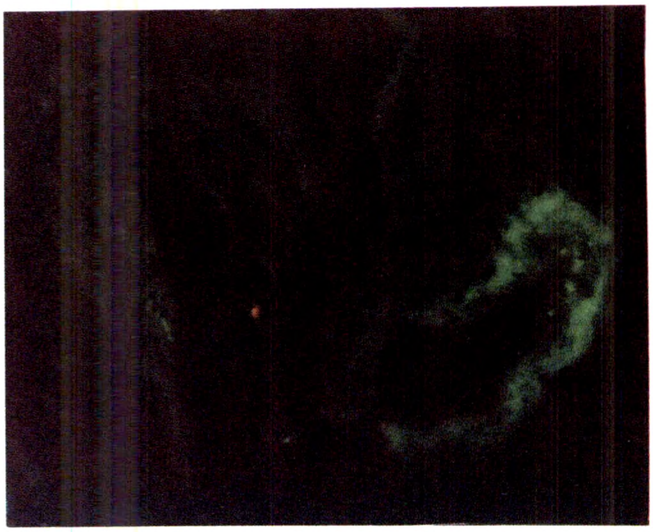

Fig 4. Immunofluorescence study of cochlear artery in type II collagen-immunized rat as shown in Fig 3. Vessel wall is thickened and shows positive reaction to rat-IgG. Similar results were obtained by using fluorescent labelled anti-C3 sera. (x1,728)

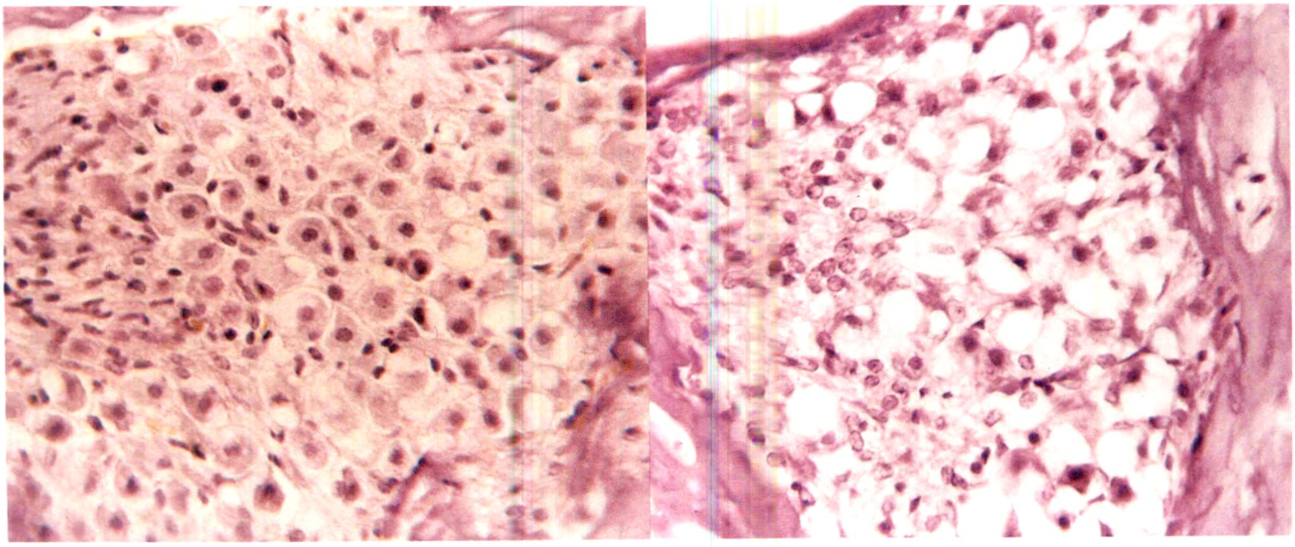

Fig. 5. A) Spiral ganglion from normal ear. B) Degenerated spiral ganglion in ear with autoimmune sensorineural hearing loss. Neurons show vacuolate degeneration in which cell bodies are swollen, cytoplasm is clear, and nuclei are pyknotic and displaced toward two axonal poles of cells. Nerve fiber shows slight decrease in number. (x2,304)

TABLE 2. RESULTS OF CALORIC TEST FOR VESTIBULAR FUNCTION*

Animal	*Response in Total Tests*	*Average Duration of Nystagmus in Responding Rat*
Normal	7/7	22 s
Immunized	14/34	7.1 s

*Each ear was stimulated by infusion of 7 mL of cold water at 4°C. The duration of horizontal, low-amplitude, low-frequency nystagmus was measured immediately following infusion.

TABLE 3. PERIVASCULAR DISORDER OF COCHLEAR ARTERY IN NORMAL AND COLLAGEN-IMMUNIZED RATS

	Normal (N = 10 Ears)		*Collagen-Immunized (N = 23 Ears)*	
	—	+	—	+
Perivasculitis	8	2	2	21
Arterial wall thickening	7	3	11	12
Mononuclear cell infiltration	8	2	3	20
Perivascular fibrosis	9	1	6	17

Table 2 shows the results of caloric testing. Among 17 rats tested, eight had bilateral failure to respond while five had unilateral failure. In those showing some response, the duration was diminished as compared to control rats.

Histopathologic studies were performed on the inner ears of both experimental and control rats. Perivascular abnormalities were observed in the cochlear artery (Table 3 and Fig 3). A large number of mononuclear cells had infiltrated around the artery; the vessel was thickened and endothelial cells were increased. Mild fibrosis was found in the perivascular area. Immunofluorescence revealed the deposition of green fluorescent substances in the vessel wall, perivascular fibrous tissue, and surrounding bone tissue of the cochlear artery in all rats. In the vestibular artery, the carotid artery or a large vessel that runs through the temporal bone, the mononuclear cell infiltration was mild with perivascular fibrosis. The immunofluorescence study, however, detected that green fluorescent substances were also deposited in the perivascular fibrotic tissue of these vessels in the immunized animals, but not in the control animals. No pathological changes were seen in the area of small vessels or capillaries in regular H & E-stained or immunofluoresence sections (Fig 4).

Spiral ganglion cell degeneration was also observed (Fig 5). There was vacuolate degeneration of the cochlear neurons throughout most of the cochlea of the type II collagen-immunized rats. The ganglion cell bodies were swollen, the cytoplasm clear, and the nuclei were pyknotic and displaced toward the axonal poles of the cells. Nerve fibers showed slight atrophic changes. Pathological changes were relatively conspicuous in the apical turn relative to the basal turn. In the apical turn, 50% or more of the spiral ganglion cells were degenerated in 16 of 23 rats with type II collagen-induced hearing loss, while in the basal turn similar changes occurred in 13 of 23 rats. On the other hand, only one normal rat had vacuolate degeneration of 50% or more of the cell population (Table 4). Immunofluorescence studies did not show pathology in the area of the spiral ganglion. The organ of Corti, stria vascularis, and cochlear nerve also had normal histologies revealed on both regular H & E-stained and immunofluorescence sections. These results are from the animals immunized for less than one month's duration. However, when these animals were examined two to three months after initial immunization, we observed mild atrophic changes in the cochlear nerve, organ of Corti, and stria vascularis in 12 of 16 immunized rats. Hair cells were still present but slightly atrophied. No apparent pathological changes were observed in the vestibular sensory organ and nerve other than those previously mentioned.

Rats immunized with both type I and type II collagen had detectable antibodies to their respective immunogens. In the case of type II collagen, these antibodies were highly specific both for the type of collagen and for the native conformation (Table 5). Because of the deposition of IgG as detected by immunofluorescence, an antibody-mediated etiopathogenesis was suspected.

DISCUSSION

It has previously been shown that immunization of susceptible rats with native type II collagen results in the development of arthritis.[2] We have now shown that these animals also develop sensorineural hearing loss and vestibular disease. Evidence supports an antibody-mediated etiology for these lesions. Whether antibody of one specificity causes all these lesions is unknown. Some rats were found to have ear disease in the absence of arthritis. The presence of antibody and complement in the cochlear tissues suggests type II and/or type III immunologic mechanisms of injury, although type IV reactions may be involved. No antibody or immune complex deposition was detected in the spiral ganglion and the reason for its degeneration is unclear.

TABLE 4. SPIRAL GANGLION CELL DEGENERATION IN NORMAL AND TYPE II COLLAGEN-IMMUNIZED RATS

	Normal (N = 10 Ears)					*Collagen-Immunized (N = 23 Ears)*				
	< 10%	*30%*	*50%*	*70%*	*100%*	*< 10%*	*30%*	*50%*	*70%*	*100%*
Apical turn	9			1		1	6	12	4	
Basal turn	9			1		5	5	9	4	

< 10%-100% - Degenerated cell population in each ganglion.

TABLE 5. IgG ANTIBODY TO TYPE II COLLAGEN MEASURED BY ELISA

Animal	*Antibody (Absorbance at 450 nm)* *No Inhibition*	*Inhibition With 509 μg/m* *BII*	*DBII*	*RII*	*BI*
Collagen-immunized	1.196 ± .154	0.126	0.944	0.244	1.094
Normal	0.038 ± .008	ND	ND	ND	ND
	p < .001				

Mean values of ten rats each. Rats immunized with BII develop high levels of antibody specific for native conformation-dependent epitypes on native type II collagen. BII - Bovine type II collagen; DBII - Denatured bovine type II collagen; RII - Rat type II collagen. 1:1000 dilution of serum was used. Inhibition assay was carried out by preincubation with 50 μg/ml of inhibition collagen for 30 minutes. Antibody against BII was assayed using BII-coated plate.

Immunologically mediated injury consists of four different types of reactions. A type I reaction is an immediate hypersensitivity reaction involving IgE, seen in allergic reactions. A type II hypersensitivity is a cytotoxic reaction. The primary event in a type II reaction is that of antibody combining with an antigenic determinant which is present on tissue cells. This antigen may be part of the internal structure of the cell involved, or it may be an exogenous antigen or hapten which is absorbed on or combined with tissue cell component, and it is usually, but not always, necessary to produce cellular damage. A blood transfusion reaction is a prototype of this injury mechanism. The type III hypersensitivity reaction is mediated by antigen-antibody complexes and complements resulting in cell injury. A type IV reaction is a delayed hypersensitivity reaction involving T-cell mediated injury.

We do not know the exact cause of diminished vestibular function in those animals without apparent changes of vestibular sensory organs and nerves. It is feasible that perivascular changes observed in vestibular vessels might be a possible contributing factor; an immune injury mechanism involving cellular immunity rather than involvement of antibody or complement could be another possibility. These changes could also be due to a functional abnormality without any abnormal structural changes, as in some cases of human vestibular disorders.

The histopathologic changes noted in this animal model resemble those seen in human sensorineural hearing loss.[10] In addition, the association with hearing loss and vestibular dysfunction observed in this model mimics the early symptoms of Menière's disease. Preliminary studies performed in our laboratory also suggest that some patients with Menière's disease might have collagen autoimmunity.[11] Thus, this model may be useful in defining the pathogenesis of and identifying treatment for human deafness and vestibular disease due to autoimmunity.

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REFERENCES

1. McCabe BF. Autoimmune sensorineural hearing loss. Ann Otol Rhinol Laryngol 1979; 88:585-9.

2. Trentham DE, Townes AS, Kang AH. Autoimmunity to type II collagen: an experimental model of arthritis. J Exp Med 1977; 146:857-68.

3. Wooley PH, Luthra HS, Stuart JM, David CS. Type II collagen-induced arthritis in mice. J Exp Med 1981; 154:688-700.

4. Cremer MA, Pitcock JA, Stuart JM, Kang AH, Townes AS. Auricular chondritis in rats. An experimental model of relapsing polychondritis induced with type II collagen. J Exp Med 1981; 154:535-40.

5. Stuart JM, Cremer MA, Dixit SN, Kang AH, Townes AS. Collagen-induced arthritis in rats. Comparison of vitreous and cartilage-derived collagens. Arthritis Rheum 1979; 22:347-52.

6. Trelstad RL, Kang AH, Toole BP, Gross J. Collagen heterogeneity. High resolution separation of native [α1 (I)] 2α2 and [α1 (II)]3 and their component α chains. J Biol Chem 1972; 247:6469-73.

7. Rossi G, Solero P, Cortesina MF. Brainstem electric response audiometry. Acta Otolarynol (Stockh) 1979; Suppl 364:1-43.

8. Begleiter H, Porjesz B, Chou CL. Auditory brainstem potentials in chronic alcoholics. Science 1981; 211:1064-6.

9. Stuart JM, Townes AS, Kang AH. The immune response to collagen in type II collagen-induced arthritis in mice. J Clin Invest 1982; 69:673-83.

10. Friedmann I. Pathology of the ear. Oxford: Blackwell Scientific Publications 1974:473-90.

11. Yoo TJ, Stuart JM, Kang AH, Townes AS, Tomoda K. Type II collagen autoimmunity in otosclerosis and Meniere's disease. Science 1982; 217:1153-5.

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HEARING LOSS AFTER *HEMOPHILUS INFLUENZAE* MENINGITIS

FOLLOW-UP STUDY WITH AUDITORY BRAINSTEM POTENTIALS

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Hearing loss was studied prospectively using auditory brainstem potentials in 34 children with *Hemophilus influenzae* meningitis treated with chloramphenicol and in 36 children with purulent meningitis caused by microorganisms other than *H influenzae* treated with ampicillin. Our results indicate that high doses of ampicillin are not associated with permanent hearing loss. Moreover, no statistically significant difference was found in the incidence of hearing loss following *H influenzae* meningitis and that following meningitis caused by other microorganisms, either during the acute phase or in the convalescent period. Neurological damage, when present, was probably located in the inner ear or in the auditory nerve. Finally, early hearing loss in purulent meningitis does not always constitute an irreversible lesion.

The exact incidence of hearing loss following purulent meningitis has not been established. However, it is generally accepted that about 10% of children who suffer purulent meningitis will develop some degree of deafness, and from 5% to 20% of deaf school-age children had meningitis before the age of 2 years.[1-8]

Ampicillin has been the antimicrobial most used for therapy of purulent meningitis in the last decade with satisfactory results and very few side effects.[9,10] In 1974, Gamstorp and Klockhoff reported an increased rate of hearing loss following *Hemophilus influenzae* meningitis when treated with high doses of ampicillin.[11] Some retrospective studies supported the theory that ampicillin was responsible for the hearing loss,[12-15] while others incriminated the specificity of the different bacteria and the delay in initiation of appropriate antimicrobial therapy as the determinant factors in the genesis of postmeningitic hearing loss.[16-18]

We studied the auditory function of patients with purulent meningitis during the acute phase of the disease and after recovery to assess prospectively if hearing loss was related to the causative agent or to the type of therapy used.

MATERIAL AND METHODS

Seventy patients with purulent meningitis, aged 2 years or under, consecutively admitted to the Hospital de Pediatría, Centro Médico Nacional, IMSS, were included in this study. The patients were divided into two groups. The first group consisted of 34 patients who had *H influenzae* isolated from cerebrospinal fluid and who were treated with chloramphenicol (100 mg/kg/day) for ten days. The second group included 36 children with meningitis caused by other microorganisms *(Streptococcus pneumoniae, Streptococcus viridans, Staphylococcus aureus* and *Escherichia coli)* who were treated with ampicillin (400 mg/kg/day) for ten days.

Hearing tests were performed using the brainstem auditory evoked responses (BSAER) technique, a useful method for young children who are uncooperative with standard audiologic procedures.[19-21] Recordings were obtained using a Nicolet 1070 averager with analysis time set at 15 ms, 0.1-ms time constant of the input amplifier, and 2,048 responses to clicks averaged for each tracing. Grass P511 preamplifiers were used with an absolute gain of 10,000 and filters set at 30 to 3,000 Hz. Two tracings were obtained at each stimulus level and were recorded superimposed in order to check the replicability of each individual wave. The click stimulus was generated with nonfiltered, positive, 0.1-ms rectangular pulses, delivered through a Grason Stadler 162 speech audiometer for control of amplification and routed to either the right or the left earphone (TDH-39 with MX-41/AR cushions). Clicks were calibrated to normal hearing level in 20 normal young adults (40 ears). All patients included in this study had normal middle ears by otological microscope examination. The first recording was made between the fourth and tenth day of the acute phase of meningitis and the last one six months later, with at least one other study performed in between.

Hearing was defined as *normal* (NL) if there were wave V responses at intensity levels of less than 30 dB. Three levels of hearing impairment were considered; *minimal* (M) if no responses were seen below 30 dB but responses were evident at stimuli between 30 and 40 dB; *intermediate* (I) if no responses were evident

TABLE 1. HEARING LOSS IN 34 CHILDREN WITH *H INFLUENZAE* MENINGITIS* DURING ACUTE PHASE, IN RELATION TO INTERVAL BETWEEN ONSET OF SYMPTOMS AND INITIATION OF THERAPY

BSAER Threshold In Both Ears		*Number of Cases* Treated <48 Hours After Onset Of Symptoms	Treated >48 Hours After Onset Of Symptoms	*Total*
S	S	—	1	1
S	I	1	—	1
S	M	1	—	1
I	M	1	1	2
I	NL	1	5	6
M	M	1	2	3
NL	NL	9	11	20
Total		14	20	34

*Treated with chloramphenicol (100 mg/kg per day).
S - Severe; I - Intermediate; M - Minimal; NL - Normal.

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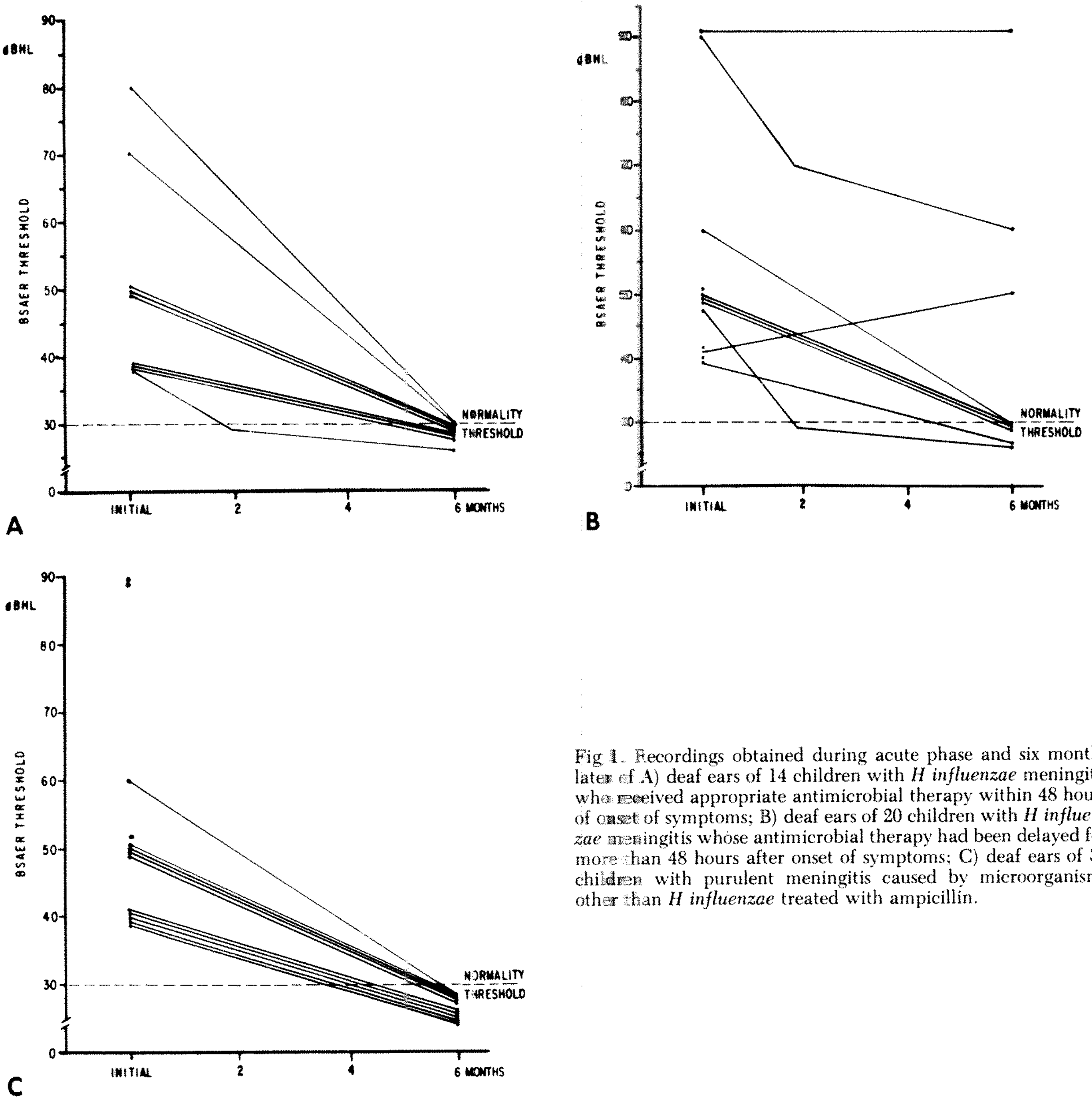

Fig 1. Recordings obtained during acute phase and six months later of A) deaf ears of 14 children with *H influenzae* meningitis who received appropriate antimicrobial therapy within 48 hours of onset of symptoms; B) deaf ears of 20 children with *H influenzae* meningitis whose antimicrobial therapy had been delayed for more than 48 hours after onset of symptoms; C) deaf ears of 36 children with purulent meningitis caused by microorganisms other than *H influenzae* treated with ampicillin.

at stimuli of less than 50 dB but were seen at levels between 50 and 70 dB; and *severe* (S) if wave V responses were obtained only at click intensity stimuli of 70 dB HL or greater. If no responses were seen to click stimuli of the greatest intensity available (100 dB), the result was called *no response*. Statistical analysis of the results was made using the chi-square and Fisher's test.

RESULTS

Initial Hearing Evaluation. Fourteen of the 34 patients (41.2%) with meningitis due to *H influenzae* treated with chloramphenicol had some degree of hearing impairment at the time of their first evaluation with disappearance of not only wave V, but all other recordable waves as well (Table 1). No differences were found between the 14 patients who received appropriate antimicrobial treatment within 48 hours of symptoms and the 20 patients whose treatment was begun later. Hearing loss was bilateral in eight patients and unilateral in six patients with a total involvement of 22 ears (Fig 1A,B).

Eight of the 36 (22.2%) patients with meningitis caused by microorganisms other than *H influenzae* and who were treated with ampicillin had some initial hearing loss (Table 2). Four of these patients had bilateral and four had unilateral impairment, with a total of 12 affected ears (Fig 1C). The incidence of acute hearing loss in patients with meningitis due to *H influenzae* and patients with meningitis due to other microorganisms was not significantly different.

Follow-up Hearing Evaluation. All initial normal hearing tests were normal six months later. Two of the 22 patients with initial hearing loss died and two failed to return for further hearing tests. The initial tests in these patients showed bilateral in-

TABLE 2. HEARING LOSS IN 36 CHILDREN WITH MENINGITIS* CAUSED BY ORGANISMS OTHER THAN *H INFLUENZAE* DURING ACUTE PHASE AND SIX MONTHS LATER

BSAER Threshold In Both Ears		*No. of Cases at Time of Evaluation*	
		Acute Period	*6 Mo Later*
S	S	1	—
I	M	2	—
I	NL	3	—
M	M	1	—
M	NL	1	—
NL	NL	28	34
Total		36	34

*Treated with ampicillin (400 mg/kg per day).

TABLE 3. PERMANENT HEARING LOSS* IN 12 CHILDREN WITH *H INFLUENZAE* MENINGITIS IN RELATION TO INTERVAL BETWEEN ONSET OF SYMPTOMS AND INITIATION OF THERAPY

BSAER Threshold In Both Ears		*Number of Cases*		
		Treated <48 Hours After Onset Of Symptoms	*Treated >48 Hours After Onset Of Symptoms*	*Total (Cases)*
S	I	—	1	1
I	NL	—	1	1
NL	NL	5	5	10
Total		5	7	12

*Six months later.

volvement in those who died (severe-severe [S-S], intermediate-intermediate [I-I] and unilateral involvement in the other two (intermediate-normal [I-NL], normal-intermediate [NL-I]). Of the remaining 12 children with initial hearing loss due to *H influenzae* meningitis treated with chloramphenicol, ten had normal follow-up recordings, while in two, the loss remained unchanged. These two patients have been followed for two years, and in both the hearing impairment persists, one with a unilateral problem and the other with bilateral involvement; the final test results were the same as the initial ones (Table 3). Both children had their antimicrobial treatment started after 48 hours of onset of symptoms but there was no statistical difference in the chance that they would acquire a hearing loss when compared to patients who received treatment within 48 hours of onset of the disease. The remaining six initially deaf patients who had meningitis due to microorganisms other than *H influenzae* and who were treated with ampicillin completely recovered their hearing function (Table 2). The incidence of permanent hearing loss in the two groups of patients was not statistically different.

DISCUSSION

Because of the recent emergence of 13% of ampicillin-resistant *H influenzae* strains in our community,[22] we use chloramphenicol (accompanied initially by sodium penicillin until the etiology is confirmed) for the treatment of *H influenzae* meningitis. This clinical material and the availability of a reliable technique for the evaluation of auditory function in young children prompted us to study the relationship between the etiology of meningitis, antimicrobial therapy, and permanent hearing loss.

Our results suggest that high doses of ampicillin, as used in patients with meningitis caused by microorganisms other than *H influenzae*, are not associated with permanent hearing loss, an observation that supports previous retrospective reports.[16-18] Furthermore, there was no statistically significant difference in the incidence of either acute or persistent hearing loss in patients with meningitis produced by *H influenzae* and that caused by other microorganisms. When hearing loss was present, it consisted of disappearance of all recordable waves (I-VII). This suggests that the inner ear or the auditory nerve is damaged.[21] It appears that inner damage is produced by diffuse inflammation of the subarachnoid space with local arachnoiditis in the auditory canal, leading to neuritis and perineuritis of the eighth nerve.[23] The damage to other cranial nerves (III, IV, VI and VII) found in 1.8% of the cases in patients with purulent meningitis[24] supports this pathogenetic hypothesis, as does the fact that most often the BSAER abnormalities reverted to normal after successful medical management of the meningitis. This hypothesis may also be relevant to the observations of Richner and Prader,[18] who found that early treatment of *H influenzae* meningitis was less frequently associated with hearing loss than those cases where treatment was delayed for more than 48 hours. Therefore, it was suggested that intense, persistent, and diffuse inflammation of the meningeal coverings at the base of the brain entails a higher risk of cranial nerve damage following bacterial meningitis. In our study, although it was not statistically significant, the only two children with permanent hearing loss following *H influenzae* meningitis had their initial treatment delayed beyond 48 hours of the appearance of symptoms.

All but two of the 18 patients with initial hearing impairment that could be followed in our survey had recovered normal hearing by six months, confirming Roesner and Campbell's observation[25] that initial hearing loss in bacterial meningitis is usually reversible.

Finally, some consideration should be given to the question of whether BSAER to wide-band clicks actually measures "hearing." First, the click stimulus activates all portions of the cochlea, generating waves that travel the entire length of the basilar membrane. However, because of the increasing loss in velocity there are cumulative time delays imposed on the responses of fibers originating in the upper segments of the cochlea. Therefore, only the activity generated in the basal part has sufficient neural units synchronized to produce a significant compound, far-field, volume-conducted response. There is evidence in the click-evoked responses of activity generated at the 2,000 Hz level and perhaps a little lower. No activity can be measured in response to stimuli of 1,000 Hz or lower frequencies. The second question is whether measuring electrical activity at the lower levels of the auditory pathway (up to the inferior colliculus) is equivalent to measuring the sensation of hearing, which is a cortical phenomenon of a psychological nature. Although they are not completely equivalent, electrical activity can be considered a fairly reliable index of physiological function, especially at the lower levels of the auditory pathway.

With these two limitations in mind, we still believe that BSAER can detect gross peripheral hearing abnormalities in patients who, because of either their age or their clinical condition, could not be tested by other methods. Whenever possible, however, traditional psychoacoustical testing should be carried out.

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REFERENCES

1. Teng Y-C, Liu JH, Hsu Y-H. Meningitis and deafness. Report of 337 cases of deafness due to cerebrospinal meningitis. Chinese Med J 1962; 81:127-30.

2. Bergstrand CG, Fahlén T, Thilen A. A follow-up study of children treated for acute purulent meningitis. Acta Paediatr 1957; 46:10-7.

3. Landthaler G, Andrieu-Guitrancourt J. Contribution a l'etude des ataxis et des surdites secondaries aux meningites purulent de l'enfant. Ann Oto-Laryngol 1974; 91:293-309.

4. Vernon M. Meningitis and deafness: the problem, its physical, audiological, psychological, and educational manifestation in deaf children. Laryngoscope 1967; 77:1856-74.

5. Nadol JB. Hearing loss as a sequel of meningitis. Laryngoscope 1978; 88:739-55.

6. Dodge PR, Swartz MN. Bacterial meningitis. A review of selected aspects. N Engl J Med 1965; 273:1003-9.

7. Bresky B, Buchbinder S, Geenberg IM. The incidence of neurologic residua in children after recovery from bacterial meningitis. Arch Pediatr 1962; 79:63-71.

8. Barton ME, Court SD, Walker W. Causes of severe deafness in school children in Northumberland and Durham. Br Med J 1962; 1:351-5.

9. Hambleton G, Davies PA. Bacterial meningitis. Some aspects of diagnosis and treatment. Arch Dis Child 1975; 50:674-82.

10. Muñoz O. Cantú J, Trejo-Pérez JA, Fierro H. Meningoencefalitis purulenta. I. Etiología y tratamiento antibiótico. Gac Med Mex 1979; 115:89-91.

11. Gamstorp PI, Klockhoff I. Hearing loss after *H influenzae* meningitis. Dev Med Child Neurol 1975; 17:119-20.

12. Jones FE, Hanson DR. *H influenzae* meningitis treated with ampicillin or chloramphenicol, and subsequent hearing loss. Dev Med Child Neurol 1977; 19:593-7.

13. Koskiniemi M, Pettay O, Raivio M, Sarna S. *Hemophilus influenzae* meningitis. A comparison between chloramphenicol and ampicillin therapy with special reference to impaired hearing. Acta Paediatr Scand 1978; 67:17-28.

14. Raivio M, Koskiniemi H. Hearing disorders after *Haemophilus influenzae* meningitis. Arch Otolaryngol 1978; 104:340-4.

15. Nylen O, Rosenhall V. *Haemophilus influenzae* meningitis and hearing. Int J Pediatr Otorhinolaryngol 1979; 1:97-101.

16. Svenvagsson B, Bengtsson E, Fluur E, Siegborn J. Hearing loss as a sequel to chloramphenicol and ampicillin treatment of *Haemophilus influenzae* meningitis. Scand J Infect Dis 1976; 8:175-80

17. Dahnsjö H, Andersson H, Hallander HO, Ruoberg RD. Tone audiometry control of children treated for meningitis with large doses of ampicillin. Acta Paediatr Scand 1976; 65:733-7.

18. Richner B, Prader HA. Hearing impairment following therapy of *Haemophilus influenzae* meningitis. Helv Paediatr Acta 1979; 34:443-7.

19. Stockard JJ, Rossiter VS. Clinical and pathologic correlates of brain stem auditory response abnormalities. Neurology 1977; 27:316-25.

20. Mizrahi EM, Dorfman LS. Sensory evoked potentials: clinical applications in pediatrics. J Pediatr 1980; 97:1-10.

21. Cody DT. Cortical evoked responses in neuro-otologic diagnosis. Arch Otolaryngol 1973; 97:96-103.

22. Guiscafré H, García-Melgar M, Muñoz O. Screening for ampicillin resistant *Hemophilus influenzae* and penicillin resistant *Str pneumoniae* in healthy carriers. Arch Invest Med (Méx) 1981; 12:141-51.

23. Keane WM, Potsic WP, Rowe LD, Konkle DF. Meningitis and hearing loss in children. Arch Otolaryngol 1979; 105:39-44.

24. Muñoz O, Cantú J, Trejo JA, Fierro H. Meningoencefalitis purulenta. II. Complicaciones de la fase aguda y su manejo. Secuelas y pronóstico. Gac Med Méx 1979; 115:91-4.

25. Roesner RJ, Campbell JC. Recovery of auditory function following meningitis deafness. J Speech Hear Dis 1975; 40: 405-1[illegible].

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FREQUENCY SELECTIVITY AND TEMPORAL PROCESSING IN FRIEDREICH'S ATAXIA

CLINICAL ASPECTS IN TWO PATIENTS

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We performed psychoacoustical tuning curves and measured temporal summation in two patients with Friedreich's ataxia to study aspects of frequency selectivity and temporal processing in the auditory system. In the majority of frequencies tested, normal psychoacoustical tuning curves and unimpaired temporal summation functions were obtained. These findings suggest that the processing mechanism responsible for these phenomena is intact.

INTRODUCTION

Friedreich's ataxia is a hereditary, progressive, and degenerative neurological disorder. Its onset occurs before puberty, producing ataxia, dysarthria, weakness, areflexia and proprioceptive deficits. The dorsal root ganglion (DRG) is a major site of neuronal degeneration where large neurons are predominantly affected. The large neurons of the DRG are the parent cells that mediate proprioception centrally. Their axons reach skin and joint receptors distally and terminate in gracile and cuniate nuclei centrally, after traveling in the dorsal columns of the spinal cord.

Peripheral nerve sensory action potentials (SNAPs) are either absent or grossly diminished in amplitude in these patients. This physiological abnormality has been attributed to loss of the supporting parent cell in the DRG with distal axonal atrophy. We found marked abnormalities in the brainstem auditory evoked potentials (BAEPs) in five patients with Friedreich's ataxia.[1,2] The BAEPs either were absent or had no recognizable waveforms. We explained these findings on the basis of a neuronal loss or dysfunction in the spiral ganglion (Sp G). There is support for this view from various sources. Another disease, Charcot-Marie-Tooth disease (CMT) where DRG cell loss occurs also shows BAEP abnormalities.[2,3] Morphological support for Sp G cell loss exists in the literature in two autopsied cases of Friedreich's ataxia.[4] Furthermore, there is evidence for evoked potential abnormalities existing in other sensory pathways. In two recent studies, visual and somatosensory evoked potentials exhibited marked abnormalities in Friedreich's ataxia patients.[5,6] Significantly, none of our patients complained of hearing difficulties in spite of these gross evoked potential and behavioral auditory test abnormalities we reported previously[1,2] (see Discussion for details). Thus, Friedreich's ataxia presents an unusual clinical setting to assess auditory functions in a system that lacks a major afferent cell station in its pathway.

To study aspects of frequency selectivity and temporal processing ability in this group, we performed psychoacoustical tuning curves (PTCs) and measurements of temporal summation (TS) in addition to many other tests. The PTCs and TS functions are process-oriented tests which may further our understanding of possible underlying mechanisms mediating these processes in humans. Both tests are noninvasive and have not been reported previously in these patients.

METHODS

Both subjects (man, 30 years; woman, 33 years) in this study received complete audiological testing with previously reported methods.[1]

Psychoacoustical tuning curves were generated using a simultaneous masking paradigm with a fixed-frequency tracking method to obtain all masked thresholds. The attenuation rate was 2 dB/s. The probe tone was fixed at a characteristic frequency and the masking frequency was varied. Probe-tone frequencies consisted of pure-tone stimuli of 0.5, 1, and 2 kHz and durations of either 10, 20, 50 or 200 ms specified at half power points. The rise and fall time of the probe tone was 10 ms specified as the time between 10% and 90% of the maximum amplitude of the signal envelope. Probe-tone repetition rate was one per second for all durations so the expectancy rate was constant for all tones. Masked thresholds were established on the basis of 30 to 60 seconds of standard tracking after tracking stabilized. Thresholds were defined as the midpoints of the tracking excursions. Prior to the generation of the PTCs, behavioral thresholds were reassessed and measurements of TS were made.

Measurements of TS were made at each frequency (0.5, 1, and 2 kHz), following the methodology described by Wright.[7]

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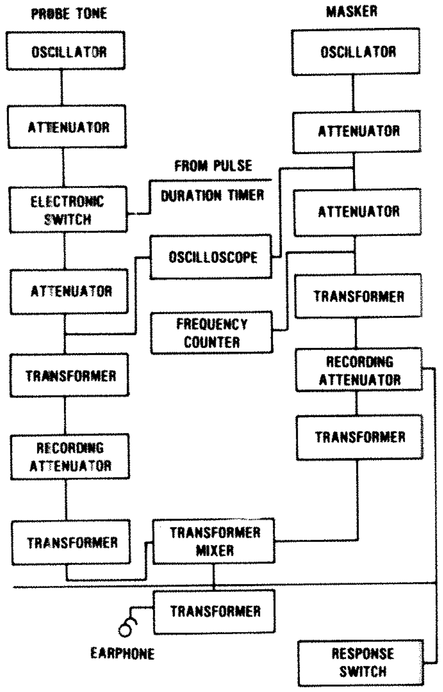

Fig 1. Block diagram representing instrumentation utilized to obtain PTCs and TS measurements.

Instrumentation. For PTC implementation, the probe-tone and masker signals were produced by two independent oscillators (Hewlett-Packard, models 241A and 200ABR). Each signal was then sent to the separate power attenuator (Hewlett-Packard, model 350D). From the power attenuator, the probe tone was sent to an electronic switch (Grason-Stadler, model 1287B) that provided the appropriate pulse characteristics and then to a 2-dB step attenuator (Daven, 1%). From there both signals were sent to separate recording attenuators (Grason-Stadler, model 3262A) and returned to a transformer-mixer where the pulse probe tone and continuous masker were combined. From the mixer, the signals were sent to an earphone (Telephonics, model TDH-39) mounted in a supra-aural cushion (MX41/AR). The earphone was located inside the sound-treated room with a response switch. The frequency of the masker was continuously monitored with a frequency counter (Hewlett-Packard, model 5223L). The waveforms of the masker and probe tone were monitored continuously on separate channels of a multichannel oscilloscope (Tektronix model 3A74, Fig 1).

RESULTS

The results can be seen in graphic form in Figures 2 and 3 and in tabulated form in the Table.

All PTCs and TS functions except one (patient 2, at 0.5 kHz) were normal in appearance. The data indicated 1) normal, low-threshold, sharply tuned tip segments (Q_{10} range 5 to 8), 2) low-frequency tail segment exceeding 35-dB/octave slope (range 37 to 52 dB) and, 3) the high-frequency tail segment exceeding 110-dB/octave slope (range 112 to 228 dB). Normative comparisons were made utilizing identical methodology from the parametric study reported by Grimes and Wright.[9] In the majority of frequencies tested, the low-threshold sharply tuned tip segment and the high-and low-frequency tail segments were preserved and considered normal. At one frequency (patient 2, at 0.5 kHz), an auditory threshold of 55 dB SPL could have accounted for a PTC which was not sharply tuned and a truncated TS function indicating a cochlear lesion. Additionally, in all instances where PTCs were normal, TS functions were also normal. Thus, these data support normal aspects of frequency selectivity and temporal processing abilities in the majority of frequencies tested.

DISCUSSION

We have previously published audiological data concerning patients with Friedreich's ataxia.[1] Audiological findings from these two patients can be seen in Figure 4. Normal auditory sensitivity or, at most, a moderate sensitivity loss at some frequencies, absent or unrecognizable BAEPs, Performance Intensity Functions for Phonetically Balanced Words (PI-PB) showing the roll-over phenomenon, minimal performance deficit in the Synthetic Sentence Identification in the Ipsilateral Competing Message (SSI-ICM) but normal performance in the SSI-Contralateral Competing Message (CCM) mode, and abnormal acoustic reflex measurements were noted. Viewed as a whole,

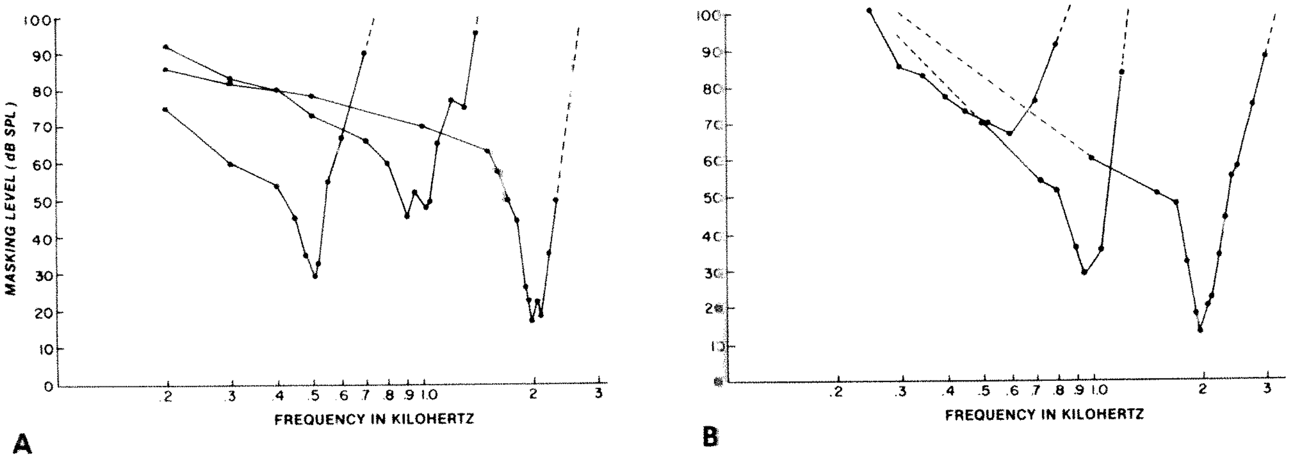

Fig 2. A) Normal PTC data obtained from left ear in patient 1 (female, 33 years) at 0.5, 1, and 2 kHz. B) Normal PTC data obtained from left ear in patient 2 (male, 30 years) at 1 and 2 kHz. Curve obtained at 0.5 kHz is broadly tuned and considered abnormal.

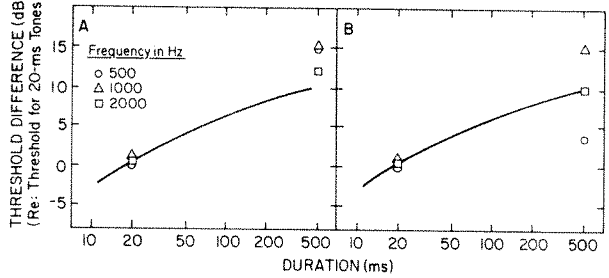

Fig 3. A) Temporal summation results for patient 1 revealing unimpaired temporal summation at 0.5, 1 and 2 kHz. B) Results for patient 2 revealing unimpaired temporal summation at 1 and 2 kHz. Truncated temporal summation function obtained at 0.5 kHz is considered abnormal and suggestive of cochlear involvement. Temporal summation measurements were obtained by comparing relative threshold difference in decibels between 500-20 ms tones. Solid black line represents theoretical normal temporal summation function.[8]

these findings suggest primarily a first order neuron (eighth nerve) site of lesion.

The pathophysiology of this disorder involves the DRG where large neurons undergo degeneration. Probably, a similar neuronal loss or, at least, dysfunction occurs in the Sp G, also. We view the degeneration of DRG and Sp G neurons as parallel processes. Electrophysiological findings are similar, that is, absent or grossly diminished SNAPs and absent or unrecognizable BAEPs. Histopathologic findings of extensive Sp G degeneration in two autopsied patients with Friedreich's ataxia[4] are noteworthy since the outer spiral fibers destined for the outer hair cells appeared to be preserved. This corresponds to the findings in animal experiments where outer spiral fibers did not degenerate after transection of the cochlear nerve, even though the myelinated portion of about 95% of the cochlear neurons and spiral ganglion cells had disappeared. Thus, this disorder seems to naturally simulate the auditory nerve degeneration studies reported by Spoendlin and Gacek.[10] Given these findings, our purpose was to determine the effect of this disorder on frequency selectivity and temporal summation in order to define better the auditory processing ability of such patients. We shall review pertinent literature first before providing an explanation for our findings.

Tuning curves have been used increasingly to demonstrate frequency selectivity in the auditory system. These measures can be obtained from single unit recordings,[11] using compound action potentials,[12] and by psychoacoustical methods.[13] The latter may reflect a process similar to its physiological counterpart. In one view, frequency selectivity is thought to be a peripheral event, mediated by a two-stage filtering process,[14] a low-pass mechanical first filter reflective of the basilar membrane and a subsequent second filter responsible for low-threshold, sharp-tuning behavior. Kanamycin, Furosemide, intracochlear cyanide and hypoxia appear to have the general effect of increasing thresholds and eliminating the sharply tuned tip portions of the tuning curves.[15-17] Evans proposes that these agents impair the metabolically labile second filter, leaving intact the mechanical filtering properties of the basilar membrane. This results in broadly tuned curves. Siegel and Kim[18] also support a peripheral basis for frequency selectivity and sensitivity. However, they attribute this process to the bidirectionally coupled motion of the cochlear partition emphasizing this to be a metabolically dependent, biomechanical process.

Frequency selectivity has also been studied from an ontogenetic perspective. Carlier et al[19] showed that sharply tuned curves were not seen in kitten and rat pups until functional maturation of outer hair cells occurs in the organ of Corti. However, Saunders et al[20] suggest that in the mouse, the development of afferent dendritic synaptic contacts with the inner hair cells accounts for the reported development of frequency selectivity.

Morphological diversity at the hair-cell and neuronal level of the auditory system is well documented.[21] Outer hair cells may be responsible for low level threshold behavior,[22] and in many animals, an elevation of absolute hearing sensitivity occurs after selective elimination of outer hair cells.[23,24] However, single unit data elicited from the eighth nerve fail to demonstrate two populations of fibers having different thresholds.[11,25]

Bilger's suggestion[26] that TS may reflect the integrity of outer hair cells is supported by anatomical

TABULATED PSYCHOACOUSTICAL TUNING CURVE AND TEMPORAL SUMMATION DATA

		Patient 1			Patient 2	
Tuning Curve Components	*500 Hz*	*1000 Hz*	*2000 Hz*	*500 Hz*	*1000 Hz*	*2000 Hz*
Tail (dB/octave slope)						
Low frequency tail	37	44	52	31	48	42
High frequency tail	122	112	202	44	228	122
Q_{10}*	6.3	5	8	1.6	6.6	8
Probe tone sensation level (dB)	10	10	10	10	25	15
Probe tone duration (ms)	10	50	10	20	200	200
Unmasked threshold (dB SPL)	28	32	4	55	15	10
Temporal summation (dB)†	15	15	12	4	15	10

*Q_{10} was derived by dividing the probe-tone frequency by the bandwidth of the tuning curve 10 dB above the masked threshold at the characteristic frequency.

†Temporal summation functions were elicited comparing the threshold differences in decibels between 500 ms- and 20 ms- duration tones.

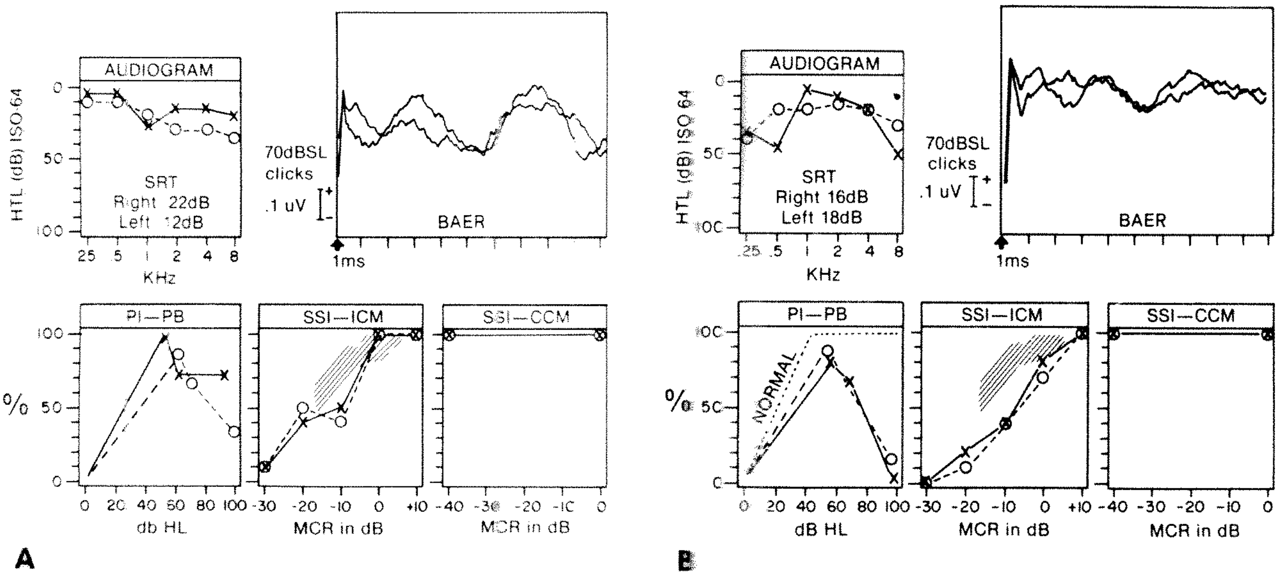

Fig 4. A, B) Audiometric test results of patients 1 and 2. Normal auditory sensitivity or, at most, moderate sensitivity loss at some frequencies, absent or unrecognizable BAEPs (left ear results depicted in both diagrams). PI-PB rollover phenomenon, minimal performance deficit in the SSI-ICM and normal performance in the SSI-CCM modality, and abnormal acoustic reflex measurements. (Reprinted with permission.[1])

evidence. Outer hair cells are more susceptible than inner hair cells to the effects of noise exposure[27] and TS is disrupted by even mild exposures to sound.[23-31]

Cochlear microanatomy research is of particular interest to frequency selectivity. It has identified the presence of stiff stereocilia in the hair cells. The stereocilia are, in part, composed of actin filaments.[32-34] The actin filaments, in addition to providing a mechanical tuning capability, may also be metabolically regulated.[35] Additionally, the cytoarchitecture of the chinchilla inner hair cell is thought to be maintained by the striated organelle (Friedman body) present in the infracuticular plate region of these cells. They may provide directional orientation for the stereocilia by controlling contractile proteins.[36,37] The tallest stereocilia of the outer hair cells are attached to the tectorial membrane.[38,39] Harris[40] has suggested that a change from a stiff to a loose coupling of the hair cell stereocilia to the tectorial membrane can elevate auditory sensitivity by as much as 55 dB. Tonndorf[41] has extended this hypothesis and suggests that dysfunction of the hair cell stereocilia decouples the involved hair cells from the tectorial membrane causing sensory hearing loss, recruitment, poor speech discrimination and tinnitus.

With the above review as a basis, we offer these explanations for the findings in our patients. The preservation of sharply tuned PTCs and relatively intact pure-tone sensitivity appear to indicate that the sensory processing mechanism responsible for these phenomena is intact. Within this context, the favorable speech discrimination (PB max) and the performance on other speech tests utilized (Fig 4) may also be in agreement with a sharply tuned peripheral system as revealed by our PTCs. It was also observed that by increasing the intensity variable in speech discrimination testing, a dramatic decrease in performance resulted, producing the PI-PB rollover phenomenon. This finding suggests that a reduction in channel capacity may occur as a result of depopulation of Sp G neurons.

The lack of synchronous, well-developed BAEPs and the histopathologic findings reported by Spoendlin[4] also lead us to believe that in our patients, significant dysfunction exists at the level of the Sp G. As a result, the neural elements needed to mediate the precise timing and synchrony for well-developed BAEPs are compromised.

In summary, the psychoacoustic and electrophysiologic data strongly suggest a peripheral eighth nerve site of lesion in these patients. This is in agreement with the results obtained on two autopsied patients.[4] Auditory functions, ie, temporal summation and frequency selectivity, that are believed to be preconditioned on normal spatial summation (normal outer hair cell function), are psychoacoustically normal in these patients. Hence, structure and function of outer hair cells and innervating fibers appear to be unaffected, yet derangement at a more proximal level (Sp G), can be demonstrated. We believe that these findings are supportive of an interactive relationship between inner and outer hair cells. We propose that appropriately chosen Friedreich's ataxia patients may serve as a clinical model for studying such interaction.

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REFERENCES

1. Satya-Murti S, Cacace AT, Hanson PA. Auditory dysfunction in Friedreich ataxia: result of spiral ganglion degeneration. Neurology 1980; 30:1047-53.

2. Satya-Murti S, Cacace AT. Brainstem auditory evoked potentials in disorders of the primary sensory ganglion. In: Courjon J, Mauguire F, Revol M, eds. Clinical applications of evoked potentials in neurology. New York: Raven Press, 1982:219-25.

3. Stockard JJ, Stockard JE, Sharbrough FW. Brainstem auditory evoked potentials in neurology: methodology, interpretation, clinical application. In: Aminoff MJ, ed. Electrodiagnosis in clinical neurology. London: Churchill Livingston, 1980:370-413.

4. Spoendlin H. Optic and cochleovestibular degenerations in hereditary ataxias. II. Temporal bone pathology in two cases of Freidreich's ataxia with vestibulo-cochlear disorders. Brain 1974; 97:41-8.

5. Carrol WM, Kris A, Baraiter M, Barret G, Halliday AM. The incidence and nature of visual pathway involvement in Friedreich's ataxia. A clinical and visual evoked potential study of 22 patients. Brain 1980; 103:412-34.

6. Pedersen L, Trojaborg W. Visual, auditory and somatosensory involvement in hereditary cerebellar ataxia, Friedreich's ataxia and familial spastic paraplegia. Electroencephalogr Clin Neurophysiol 1981; 52:283-97.

7. Wright HN. Clinical measurement of temporal auditory summation. J Speech Hear Res 1968; 11:109-27.

8. Zwislocki J. Theory of temporal auditory summation. J Acoust Soc Am 1960; 32:1046-60.

9. Grimes CT, Wright HN. The influence of probe-tone parameters on the shape of psychoacoustical tuning curves in normal hearing listeners. J Speech Hear Res 1982; 25:394-401.

10. Spoendlin HH, Gacek RR. Electronmicroscopic study of the efferent and afferent innervation of the organ of Corti in the cat. Ann Otol Rhinol Laryngol 1963; 72:660-86.

11. Kiang NYS, Watanabe T, Thomas EC, Clark LF. Discharge patterns of single fibers in the cat's auditory nerve. Research monograph 35. Cambridge, Mass: MIT Press, 1965.

12. Dallos P, Cheatam MA. Compound action potential tuning curves. J Acoust Soc Am 1976; 59:591-7.

13. Small AM. Pure-tone masking. J Acoust Soc Am 1959; 31: 1619-25.

14. Evans EF, Wilson JP. Frequency selectivity of the cochlea. In: Moller AR, ed. Basic mechanisms in hearing. New York: Academic Press, 1973:519-51.

15. Kiang NYS, Moxon EC, Levine RA. Auditory nerve activity in cats with normal and abnormal cochleas. In: Wolstenholm GEW, Knight J, eds. Sensorineural hearing loss. London: Churchill, 1970:241-68.

16. Dallos P, Harris D. Properties of auditory nerve responses in absence of outer hair cells. J Neurophysiol 1978; 41:365-83.

17. Evans EF. Auditory frequency selectivity and the cochlear nerve. In: Zwicker E, Terhardt E, eds. Facts and models in hearing. Berlin: Springer, 1974:118-29.

18. Siegel JH, Kim DO. Cochlear bio-mechanics: Vulnerability to acoustic trauma, and other alterations as seen in neural responses and ear canal sound pressure. In: Hammernik R, Henderson D, Salvi R, eds. Perspectives in noise induced hearing loss. New York: Raven Press 1982:137-51.

19. Carlier E, Lenoir M, Pujol R. Development of cochlear frequency selectivity tested by compound action potential tuning curves. Hear Res 1979; 1:197-201.

20. Saunders JC, Dolgin KG, Lowry LD. The maturation of frequency selectivity in C57BL/6J mice studied with auditory evoked response tuning curves. Brain Res 1980; 187:69-79.

21. Spoendlin H. The afferent innervation of the cochlea. In: Naunton RF, Fernandez F, eds. Evoked electrical activity in the auditory nervous system. New York: Academic Press, 1978:21-39.

22. Stebbins WC, Hawkins JE, Johnson LG, Moody DB. Hearing thresholds with outer and inner hair cell loss. Am J Otolaryngol 1979; 1:15-27.

23. Ryan A, Dallos P. Effects of absence of cochlear outer hair cells on behavioral auditory threshold. Nature 1975; 253:44-6.

24. Prosen CA, Petersen MR, Moody DB, Stebbins WC. Auditory thresholds and kanamycin-induced hearing loss in the guinea pig assessed by a positive reinforcement procedure. J Acoust Soc Am 1978; 63:559-66.

25. Pfeiffer RR, Kim DO. Response patterns of single nerve fibers to click stimuli: descriptions for the cat. J Acoust Soc Am 1972; 52:1669-77.

26. Bilger RD. The audiometric profile of noise-induced hearing loss. In: Henderson D, Hamernik R, Dosanjh DD, Mills J, eds. The effects of noise on hearing. New York: Raven Press, 1976:457-65.

27. Stockwell CW, Ades HW, Engstrom H. Patterns of hair cell damage after intense auditory stimulation. Ann Otol Rhinol Laryngol 1969; 78:1144-69.

28. Jerger JF. Influence of stimulus duration on the pure tone threshold during recovery from auditory fatigue. J Acoust Soc Am 1955; 27:121-4.

29. Plomp R, Bouman MA. Relation between hearing threshold and duration of tone pulses. J Acoust Soc Am 1959; 31:749-58.

30. Bilger RC, Anderson CV. Post stimulatory fatigue and masked threshold. Abstract. J Acoust Soc Am 1961; 33:1656.

31. Henderson D. Temporal summation of acoustic signals by the chinchilla. J Acoust Soc Am 1969; 46:474-5.

32. Flock A, Cheung HC. Actin filaments in sensory hairs of inner ear receptor cells. J Cell Biol 1977; 75:339-43.

33. Tilney LG, Derosier DJ, Mulroy MJ. The organization of actin filaments in the stereocilia of cochlear hair cells. J Cell Biol 1980; 86:244-59.

34. Flock A, Cheung HC, Flock B, Utter G. Three sets of actin filaments in sensory cells of the inner ear. Identification and functional orientation determined by gel electrophoresis, immunofluorescence, and electron microscopy. J Neurocytol 1981; 10: 133-47.

35. Lim D. Cochlear anatomy related to cochlear micromechanics. A review. J Acoust Soc Am 1980; 67:1686-95.

36. Slepecky N, Hamernik RP, Henderson D. A re-examination of a hair cell organelle in the cuticular plate region and its possible relation to active processes in the cochlea. Hear Res 1980; 2:413-21.

37. Slepecky N, Hamernik RP, Henderson D. The consistent occurrence of a striated organelle (Freidman body) in the inner hair cell of the normal chinchilla. Acta Otolaryngol (Stockh) 1981; 91:189-98.

38. Engstrom H, Ades HW, Hawkins JE Jr. Structure and functions of the sensory hairs of the inner ear. J Acoust Soc Am 1962; 34:1356-63.

39. Kimura RS. Hairs of the cochlear sensory cells and their attachment to the tectorial membrane. Acta Otolaryngol (Stockh) 1965; 61:55-72.

40. Harris GG. Brownian motion in the cochlear partition. J Acoust Soc Am 1968; 44:176-86.

41. Tonndorf J. Stereociliary dysfunction, a cause of sensory hearing loss, recruitment, poor speech discrimination and tinnitus. Acta Otolaryngol (Stockh) 1981; 91:469-79.

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LASER VIDIAN NEURECTOMY

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Laser vidian neurectomy appears to offer the technical advantages of a less traumatic, more precisely controlled method of operating in an anatomical area which creates, by its location, technical difficulties in accessibility. Results indicate that postoperative patient comfort is greater, affording the opportunity to perform surgery on an outpatient basis. Results of laser vidian neurectomy are no different than those using conventional techniques.

Vidian neurectomy as a surgical treatment for the management of idiopathic vasomotor rhinitis (VMR) has become well established. But operative refinements continue to emerge because of difficulties in dissection of the pterygomaxillary space. Golding-Wood's[1] surgical technique has not proven as efficacious in the hands of other operators and alternative approaches have been successfully utilized.[2,3] The most significant advance, however, has been offered by Nomura[4] whose "transantral subperiosteal" dissection into the sphenopalatine fossa has moved the majority of the surgical dissection out of the pterygomaxillary space, away from fat, vessels, and nerves.

The operative performance of a vidian neurectomy is difficult because transsection of the vidian nerve with electrocautery must provide fine caliber suction-cautery to the vidian canal. The carbon dioxide laser as designed by Sharplan (Comment), provides an admirable solution to this situation. Not only is fine control of the laser beam possible due to the twin helium-neon aiming lights, but also the laser beam can be defocused while the aiming beams remain in focus, providing a coagulation mode essential to vaporizing the contents of the vidian canal with good hemostasis.

OPERATIVE TECHNIQUE

Under general anesthesia, the patient is positioned supine with a Richards headrest with the lateral-canthal tragis axis perpendicular to the table. The area of the incision is blocked with 2 cc lidocaine 1% with 1:100,000 epinephrine. A standard gingivobuccal incision is made down to the mucoperiosteum which is elevated to the infraorbital nerve. A McCabe antral retractor is inserted at this point. The anterior sinus wall is then removed using an 8-W laser power under a 320-mm Zeiss operating microscope objective. This empirically provides a "cutting-coagulating" laser beam approximately 1½ mm in width and allows removal of the anterior sinus wall atraumatically and hemostatically.

Approximately two square centimeters of the posterior sinus wall is then removed, paying particular attention to the junction of the posterior and medial sinus walls. The dissection is carried out from inferior to superior. The bone in this area of the sinus is dense, being composed of thin maxillary sinus bone as well as the orbital process of the palatine bones. Removal of this bone with the laser, however, is quite atraumatic, even when compared with the use of the diamond burr.

Once adequate exposure of the *medial* aspect of the pterygomaxillary space is obtained, a Montgomery pterygomaxillary elevator is used to dissect the periosteum off the pterygoid face (pterygoid process of the sphenoid bone) (Figure). Dissection must be started inferiorly and carried superiorly so that the contents of the pterygomaxillary space are elevated rostrally and laterally away from the sphenopalatine fossa. Once the dissection is complete, the surgeon can retract the contents of the pterygomaxillary space with a Montgomery elevator against the superomedial aspect of the sphenopalatine fossa (pterygoid fossa). The contents of the vidian canal emerging from the pterygoid canal are then clearly visualized.

Eight watts of laser are then used to vaporize the entire contents of the vidian canal until the complete margins of the sphenopalatine fossa are visualized. A light antral pack of antibiotic-soaked gauze is placed in the sinus. The patient is recovered for several hours in an outpatient facility and sent home.

OPERATIVE RESULTS

Twelve cases have been operated using the Sharplan carbon dioxide laser. In one case bleeding was a complication in the postoperative recovery phase. The patient was returned to surgery, the operative site reexplored, and a small vessel along the margin of the nasoantral window, which had been done conventionally with a chisel and rongeur, was cauterized. The dissection of the pterygomaxillary

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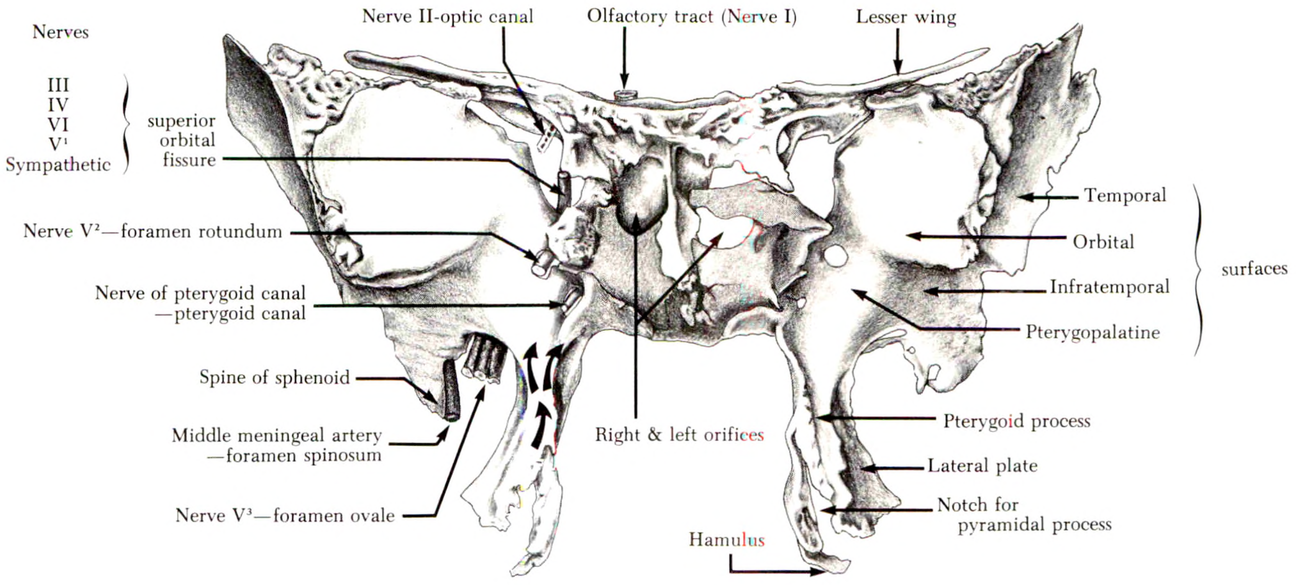

Sphenoid bone of adult, anterior aspect, with arrows depicting course of subperiosteal dissection.

space was reinspected and found to be completely dry.

All 12 patients had less pain, less swelling, and generally were more comfortable postoperatively when compared to 26 conventionally operated vidian neurectomy patients in whom chisels, rongeurs, and diamond drills were used, as well as electrocautery of the vidian nerve.

There was no significant difference in side effects. Dryness of the eye lasted three to four weeks in one patient. The transient numbness of the infraorbital and descending palatine nerves appears to be less in the laser vidian neurectomies than in conventionally operated cases, but this observation has not been quantified. The excellent reflex deturgescence of the unoperated side continues to be the rule.[3] In one case the patient did not get a good reflex on the unoperated side and a subsequent vidian neurectomy was done; a satisfactory result was not obtained. It is felt that this patient probably had alternative anatomic pathways to the nose.

COMMENT

Several companies in America, namely Coherent and Cavitron, in the mid-1960s and early 1970s, developed a carbon dioxide laser system designed primarily for use by gynecologists and laryngologists; the use and limitation of those procedures has been well documented by multiple papers by Strong in Boston.[5] The difficulty in adapting this design of laser for a laser vidian neurectomy (as well as laser tonsillectomy) is that the original decision to build the laser tube and suspend it on the microscope above the patient proved cumbersome and led to many technical difficulties. The latter have been overcome, in a large part, by the construction of a console with a laser above it and a system of articulated mirrors with an approximately 210-cm arm through which the carbon dioxide laser beam is brought from the machine to the patient. This has allowed increased flexibility in not only the handheld piece which is used for laser tonsillectomies but also in adaptation of the laser to microscopic use.

The major advantage of the Sharplan type design with an articulated arm bringing the laser beam to the microscope and/or to the patient is that the K128 coupling arm can be used in the Zeiss operating microscope system which provides a lateral tilt; ie, the scope can not only be removed in an XY plane but also in a Z axis. This allows the necessary angle to approach the pterygomaxillary space in a posteromedial direction rather than being forced in a fixed straight anteroposterior axis plane which is characteristic of the Cavitron and Coherent systems.

In the use of all carbon dioxide laser systems, it is important to have adequate aiming lights since the CO$_2$ beam is invisible. Likewise, precautions must be taken to protect the patient's corneas as well as those of the operating personnel. It is important to remember that laser energy behaves as light waves with the angle of incidence equal to the angle of reflection: flat steel objects reflect a beam that will burn holes through tissues unintentionally. While this does not present a problem in regard to the present technique of laser vidian neurectomy, we have found that in oropharyngeal and laryngeal cases, all tissues which may be subjected to the possibility of reflected laser beams should be protected with moistened gauze or neurosurgical cottonoid patties. It should also be noted that all laser machines come with a pulse as well as a continuous mode, and it is strongly recommended that the beginning surgeon, in addition to taking a course in use of the laser machine, also work in the *pulse modality only* as this will control his precision to a greater degree. The depth of any laser cut is a product of the pulse duration multipled by the power setting; in this manner, the pulse mode would guard against any untoward penetrating cuts. This is very important to remember in the posterior wall of the sinus as one does not want to inadvertently cut into the internal maxillary artery prior to removing the posterior sinus wall. As one gains technical versatility with the laser machine, the continuous mode using 8 W of laser as described in this paper can be used more safely.

REFERENCES

1. Golding-Wood PH. Observation of petrosal and vidian neurectomy in chronic vasomotor rhinitis. J Otolaryngol 1961; 75:232-47.
2. Chandra R. Transpalatal approach for vidian neurectomy. Arch Otolaryngol 1969; 89:542-5.
3. Williams JD. Transpalatal vidian neurectomy. Can J Otolaryngol 1973; 2:337-41.
4. Nomura Y. Vidian neurectomy, some technical remarks. Laryngoscope 1974; 84:578-85.
5. Strong MA, Vaughan CW, Polanyi T, Wallace R. Bronchoscopic carbon dioxide laser surgery. Ann Otol Rhinol Laryngol 1974; 83:769-76.

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SEVENTEENTH INTERNATIONAL CONGRESS OF AUDIOLOGY

The Seventeenth International Congress of Audiology will be held on August 26-30, 1984, on the University of California campus in Santa Barbara. The conference is of interest to audiologists, physicians, acousticians, engineers, and others involved with the hearing sciences. For information, direct correspondence to The Seventeenth ICA Secretariat, Speech and Hearing Center, University of California, Santa Barbara, CA 93106.

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THE DEAFNESS RESEARCH FOUNDATION — 1984 RESEARCH GRANTS

The Deafness Research Foundation invites applications for its 1984 grants in support of new research that promises to advance understanding of the causes, treatment and prevention of deafness and related ear disorders. The grants will be awarded to tax-exempt institutions for projects that will begin January 1, 1984, with the principal investigator of each project a member of the staff or faculty of such institution. The grants do not exceed $10,000, and can be competitively renewed with the same limit for an additional one or two years. Applications are reviewed for their scientific merit and for their direct or potential clinical importance.

The deadline for first-year applications is July 15, 1983; for renewal applications, August 15, 1983. For full information on the grants program, and for the required application form, please write to Grants Administrator, Deafness Research Foundation, 55 East 34th Street, New York, NY 10016.

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THYMOPHARYNGEAL DUCT CYST: A FORM OF CERVICAL THYMUS

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A unique case of a cystic thymopharyngeal duct with coexistent thymus and parathyroid glands is presented as a rare form of cervical thymus. The embryology of normal cervical descent of the thymus is reviewed. Special attention is given to the pathogenesis of a wide variety of cervical thymic tissue which may be encountered. A unifying scheme and nosology are proposed for deciphering the various reported types of solid and cystic cervical thymic abnormalities.

INTRODUCTION

More than 70 cases of both solid and cystic cervical thymus have been reported in the English literature, some with coexistent parathyroid tissue.[1] Yet rarely is cervical thymus a symptomatic cause of lateral neck mass. A spectrum of abnormalities of the thymus is attributed to the embryonic cervical descent of the thymic primordium. The abnormalities may present as a solid mass or as cystic changes in the associated epithelium derived from pharyngeal pouch endoderm.[1]

We present a unique case of a lateral neck mass composed of a cystic thymopharyngeal duct (probe patent to the pharynx) in association with an undescended solid thymus-parathyroid complex. Aside from its medical importance as a possible sole source of functioning thymic and/or parathyroid tissue, this entity has special surgical implications as a duct communicating with the pharynx.

CASE REPORT

In June 1981, a 4-year-old boy without previous history of neck mass, skin dimple, or fistula was noted to have a firm right lateral neck mass associated with a one-day fever of 39°C and bilateral posterior cervical adenopathy (Fig 1). The patient was treated with dicloxacillin, 250 mg qid for ten days; after treatment the mass was more firm, but still persisted. The patient was subsequently referred to The University of Michigan Medical Center. Initial examination showed the mass to be erythematous, firm and tender. Overlying skin remained intact. The remainder of the physical examination was normal. Laboratory workup included normal chest roentgenogram, tuberculosis skin test, and thyroid function studies. The patient continued to take the prescribed antibiotics and was scheduled for surgical exploration with the tentative clinical diagnosis of branchial cleft cyst.

Surgical exploration revealed a firm mass 2.5x2.0x1.0 cm just deep to the platysma muscle at the level of the thyroid cartilage. The mass which was adherent to surrounding soft tissue structures approximated the right lobe of the thyroid. There was no attachment to the carotid artery, jugular vein, vagus, or hypoglossal nerve. From the posterior surface of the mass, a duct 5 mm in diameter extended directly through the thyrohyoid membrane just superior to the thyroid cartilage. The duct was opened and found to be filled with clear mucus. A probe was passed through the duct and into the right pyriform sinus. The duct was ligated at the level of the thyrohyoid membrane. The patient tolerated the procedure well, without postoperative complications or recurrence of the neck mass to date.

The histomorphology of the mass revealed a persistent thymopharyngeal duct cyst with a cervical thymus-parathyroid complex (Fig 2). Specifically the histomorphology demonstrated a large central cystic duct with radial longitudinally-oriented papillary infoldings of the wall. The lining was respiratory epithelium which was hyperplastic with focal squamous metaplasia. Immediately surrounding the cystic duct was a vascular connective tissue in which was embedded normal thymus with small trapped individual thyroid follicles. In some sections the thymus and duct were in close proximity to atrophic thyroid tissue (Fig 3).

Extensions of the main cystic duct were found in adjacent connective tissue away from the main mass. Multiple tissue sections revealed that the ducts approximated solid lobules of adjacent normal thymus. There was no cystic change of Hassall's corpuscles of the thymus. In addition, the normal parathyroid gland was present within the capsule of the thymus and adjacent to the normal thyroid gland (Fig 2).

DISCUSSION

The human primordial thymus develops as ventral outgrowths of the bilateral third pharyngeal pouches around the sixth week of development (Fig 4). From the dorsal wings of these pouches the paired inferior parathyroids (parathyroid III) develop in association with the thymic primordium which elongates in a caudal and medial direction, maintaining a connection to the pharynx by hollow tubular epithelium (thymopharyngeal duct). Never does the endoderm-derived pouch communicate with the ectodermal branchial cleft (cervical sinus). This thinned upper part of the thymus has also been called the thymic cord of Hammar. Gilmour[2] maintains that the thymic cord either breaks and rapidly disappears, so that the thymus and parathyroid are separated, or that it transforms into thymic tissue so that the two glands remain connected. During the seventh week of development the epithelial connection with the pharynx is severed, the lumina are obliterated by epithelial proliferation, and the glands increase in bulk. By the eighth week, caudal

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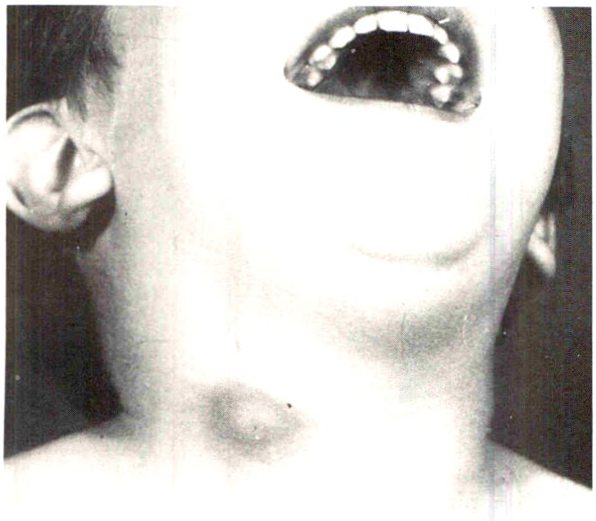

Fig 1. Four-year-old boy with right neck mass.

tips of bilateral thymus derived from the third pharyngeal pouch (thymus III) contact in the midline below the already descended thyroid gland, join the parietal pericardium, and begin their descent under the sternum to the superior mediastinum. The parathyroid III, which had been encased in the caudal tip of the thymus III, separates to remain in the connective tissue of the adjacent thyroid gland at the inferior thyroid pole. The superficially fused bilobed thymus gland takes on a lobular pattern at the third month as the thymic epithelium becomes surrounded by mesenchyme and accumulated lymphocytes.

Persistent rudiments of the epithelial ducts (canals of Kursteiner) have been described by Gilmour[2] as "vesicular, canalicular, and gland-like structures derived from the parathyroid, thymus, or thymic cord." These rudiments may give rise to cystic structures. Within the mature thymus thymopharyngeal-derived epithelium persists as the branching canalicular structures of the septae that are seen in cross section within the lobules as Hassall's corpuscles.[3] As noted by Shier,[3] the lining epithelium of the patent tubules ranges from flat, cuboidal to ciliated, tall columnar cells simulating respiratory epithelium.

The fourth pharyngeal pouch which gives rise to the paired superior parathyroids (parathyroid IV) may also give rise to a small amount of thymic tissue (thymus IV) which is thought to become incorporated into the main thymic gland, or incorporate into the thyroid gland. Occasionally it remains associated with parathyroid gland IV, which explains the not uncommon finding of thymic tissue at parathyroid exploration.[4,5]

Masses derived from the third pharyngeal pouch (pouch III) are usually adherent to the carotid sheath and pass downward lateral to the thyroid capsule and along the anterior border of the sternocleidomastoid (SCM) to the manubrium. Unlike a branchial cleft tract which would pass from the pharyngeal tonsillar fossa between the internal and external carotids, a tract from the third pharyngeal pouch would pass from the pyriform sinus through the thyrohyoid membrane, between the common carotid artery and vagus, posterior and inferior to the glossopharyngeal nerve, then downward lateral to the thyroid. On the other hand, a fourth pharyngeal pouch tract would extend from the apex of the pyriform sinus, inferiorly to the superior laryngeal nerve, externally to the recurrent laryngeal nerve, and pass inferiorly along the trachea to eventually swing forward between the arch of the aorta or the subclavian artery.

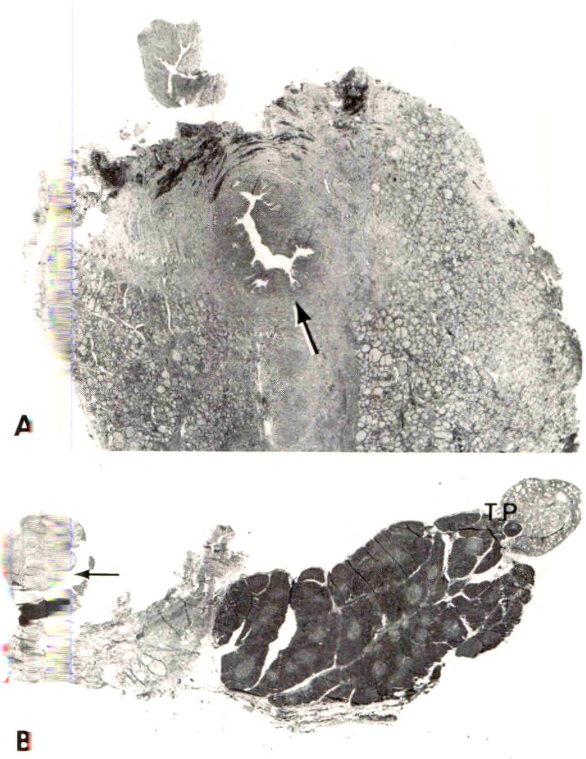

Fig 2. A) Thymopharyngeal duct (arrow) with associated inflammation, fibrosis and atrophic thyroid gland (x70). B) Thymus-parathyroid complex (TP) and adjacent thyroid gland near cystic thymopharyngeal duct (arrow) (x50).

Since the majority of the thymus gland is derived from the third pharyngeal pouch, much of the cervical thymic tissue, especially with tissue cords extending to the pharynx or mediastinum, is related to thymus III. However, discrete nodules of cervical thymic tissue may be accessory lobules of either thymus III or IV. In some instances, classification as thymus IV can be determined by anatomic localization at the posterior aspect of the thyroid capsule or by position and association with the superior parathyroid IV.[6] It is possible, however, that the parathyroid tissue associated with many discrete nodules of both thymus III and IV may be accessory in nature.

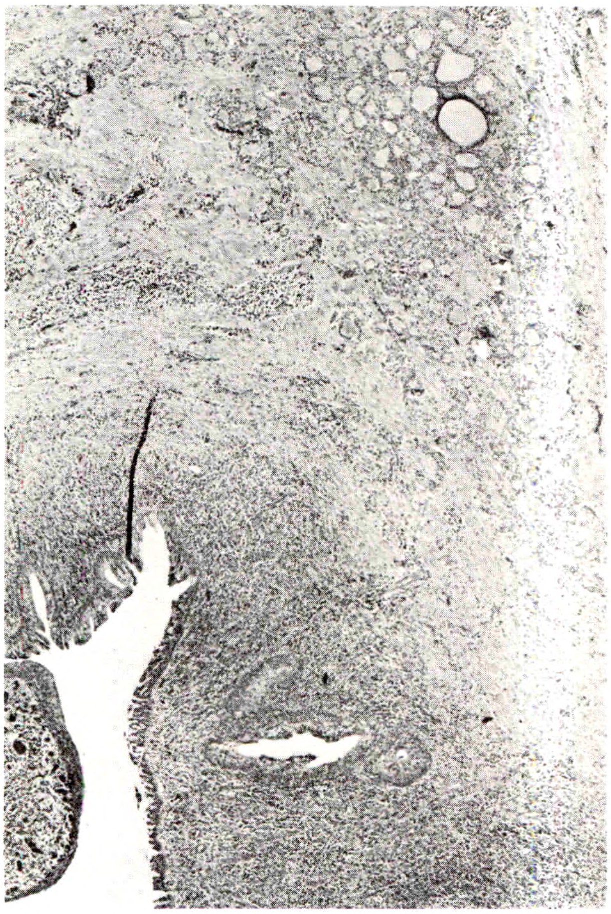

Fig 3. Cystic thymopharyngeal duct and associated inflammatory cells within dense fibrous connective tissue and atrophic thyroid gland (x175).

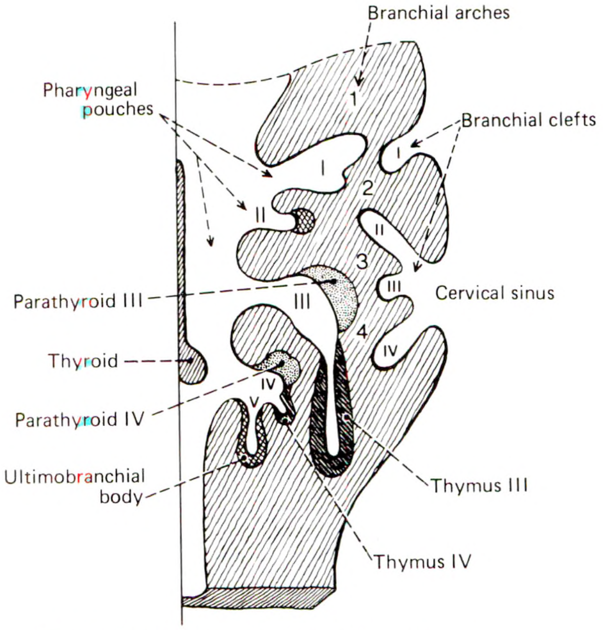

Fig 4. Section of cervical region of 6-week-old human embryo (left half, ventral view) demonstrating pharyngeal cavity, pharyngeal arches, and pouches with organ derivatives.

The pathogenesis of solid cervical thymic tissue can be divided into three major mechanisms: 1) failure of the unilateral gland to descend; 2) sequestration of accessory cervical foci of thymic tissue along the normal cervical descent pathway; and 3) failure of rostral fragments to involute or continue to descend after mediastinal descent of the majority of the gland.[1] Over the years there has been controversy regarding the etiology of cyst formation in cervical thymic abnormalities. Speer,[7] while considering cyst formation within mediastinal thymic tissue, postulated many etiologies. These included embryonal epithelial remnants, degenerating Hassall's corpuscles, infectious and inflammatory products, and neoplastic, hyperplastic, and involutional changes of the epithelial, lymphoid, or connective tissue and vascular elements of the thymus. Two dominant hypotheses seem to have emerged. One relates the pathogenesis of cystic cervical thymus to acquired progressive cystic degeneration (of unknown etiology) in Hassall's corpuscles and the epithelial reticulum of the thymus.[8-10] A second body of opinion favors cystic change in persistent unincorporated remnants of the thymopharyngeal duct.[11,12] The latter hypothesis remains the most popular and is most consistent with the developmental anatomy of the thymus. In fact this endoderm-derived epithelium, as shown by Shier,[3] continues as the cytoskeleton of the thymus, seen in the mature gland as Hassall's corpuscles. Thus it seems that cystic degeneration of vestigial extraglandular or normally occurring intraglandular tubular duct epithelium can account for the thymic cysts, whether or not the tissue is confined to the neck and/or mediastinum. Since all thymic epithelium is derived from the thymopharyngeal ducts, the distinction between the two proposed mechanisms of cyst formation is academic. Further, should cervical epithelial remnants give rise to a cystic mass without evidence of associated thymic or parathyroid tissue, it would be difficult to diagnose anything other than a congenital branchial cleft cyst. However, Mikal[13] attempted to classify thymopharyngeal duct-derived cervical thymic cysts as true thymic cysts; he classified branchial cysts with associated thymic tissue as false thymic cysts.

A wide variety of cervical thymic lesions may be encountered. Some relate anatomically to classifications of Ellis[6] and Maisel[14] of types of cervical thymus found in fetuses and young infants (Fig 5). Though many reported lesions have been solid cords of thymic tissue, the clinical presentation of many cases of cervical thymic tissue has been as cysts.[15] Some previous reports of cervical thymic cysts mention solid tissue cords unassociated with cyst formation attached to the pharyngeal wall, the thyrohyoid membrane, or extending to the mediastinum.[16-18] In contrast to sequestered solid or cystic cervical thymic tissue is the rare cystic thymopharyngeal duct persisting the length of the neck and extending to the mediastinal thymus.[19] Other cervical thymic

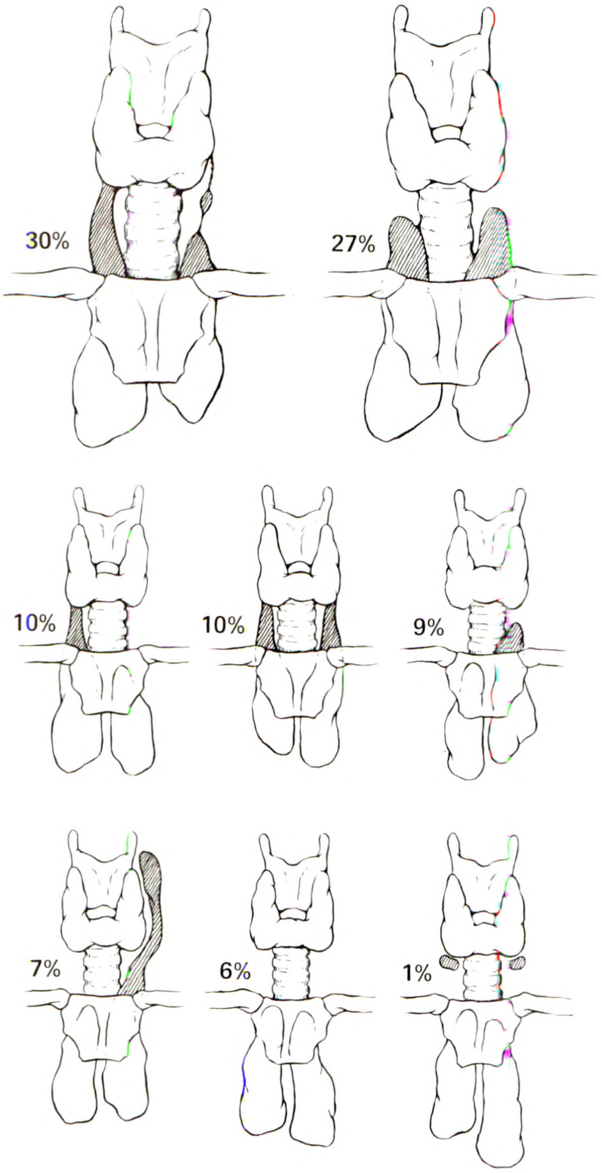

Fig 5. Incidence of fetal cervical thymus variants in descending order of occurrence. Variants are classified as unilateral/bilateral cervical prolongations of thymus which fall short, reach level of, or extend superior to thyroid gland. Discrete thymic nodules coexist with any of the variants or occur alone. Cervical thymus is not represented in the middle of bottom row. (From Ellis[8] and Maisel et al[14])

lesions include a cervical thymic cord which remains in continuity with the mediastinal thymus as well as solid thymus at the thoracic inlet.[15]

The case presented illustrates one of the earliest types of developmental arrest of thymic descent accounting for a cystic neck mass. Since it is a cystic duct associated with solid thymus extending through the thyrohyoid membrane to the pyriform sinus, it is best termed a thymopharyngeal duct cyst. In addition to the rarity of a third or fourth pharyngeal pouch cyst,[20,21] a thymopharyngeal duct cyst is unique because direct communication with the pharynx may be demonstrated on barium swallow, x-ray examination or by a water-soluble dye injected into the cystic mass preoperatively. The opportunity to trace the duct back to the pharynx is helpful in determining the embryologic origin from either pouches III or IV and may help to assess the extent of the lesion and the planned surgical repair.

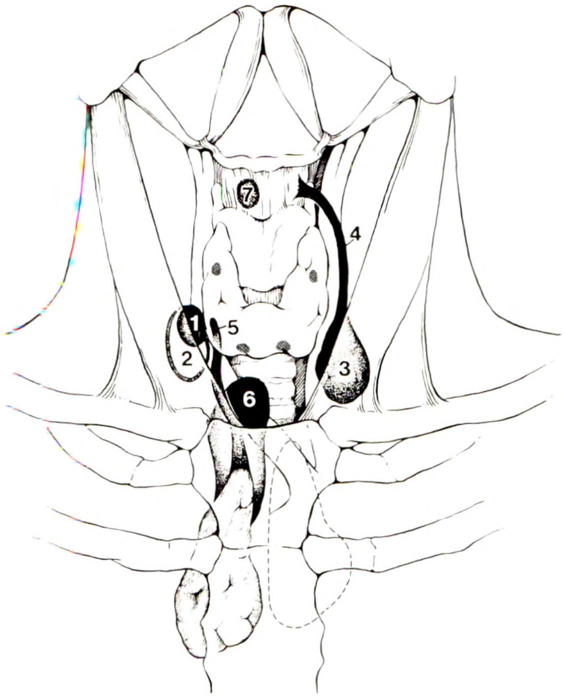

Fig 6. Anterior view of neck demonstrating seven basic forms of cervical thymus. 1 - Accessory cervical thymus; 2 - Cervical thymic cyst; 3 - Undescended cervical thymus; 4 - Persistent thymopharyngeal duct; 5 - Persistent thymic cord; 6 - Cervical extension of mediastinal thymus; and 7 - Ectopic thymus.

We propose a unifying scheme and nosology for deciphering the various reported types of solid and cystic cervical thymic abnormalities of normal embryologic migration.

The cervical thymic lesions include the following categories distinguished by anatomic location and the nature of the thymic gland tissue (Fig 6).

Accessory Cervical Thymus. Solid cervical thymic tissue is sequestered from the main gland, along the normal descent path, with or without parathyroid. Previous terms include aberrant, ectopic, undescended, persistent, or accessory thymus.

Cervical Thymic Cyst. Sequestered cystic cervical thymus is found along a normal path of descent, with or without parathyroid glands. It is a cystic version of accessory cervical thymus and may have a fibrous band or a solid thymic cord connection to the pharynx or mediastinum.

Undescended Cervical Thymus. This occurs when a solid lobe of thymus fails to descend entirely, with or without a parathyroid complex. It differs from accessory cervical thymus in that only half of the normally bilobed thymus is present in the mediastinum. Conceivably it may also become cystic.

Persistent Thymopharyngeal Duct Cyst. This is the same as undescended cervical thymus; however, the thymic duct is cystic. The thymus is solid, with or without parathyroid complex, and probably represents undescended thymus (see case report). A variant would be the cervical cystic duct leading to the mediastinal thymus.[19]

Persistent Thymic Cord. This is the cervical prolongation of a solid thymic cord which is continuous with the mediastinal thymus. The cystic variant may overlap with the histologic and clinical appearance of the cervical thymic cyst if a true connection to mediastinal thymus cannot be documented.

Cervical Extension of Mediastinal Thymus. This appears as low midline solid thymus at the thoracic inlet due to incomplete mediastinal descent. It may transiently present with increased intrathoracic pressure.[15]

Ectopic Thymus. This is the rare, solid thymic tissue in abnormal locations, eg, in the pharynx, trachea, or base of skull.[15,22] Ectopic cervical thymic cyst has not been reported.

The clinical presentation of solid cervical thymic tissue as a neck mass during the first decade of life seems to be associated with the fact that though the thymus is at its greatest relative size at birth, it reaches its greatest absolute size by puberty.[5] Reviews of cervical thymic tissue presenting as a clinical neck mass have shown a predilection for left more than right side occurrence and that males were affected more than females.[17] However, in studies of fetuses and infants, discrete nodules of cervical thymic tissue (III, IV) and cervical prolongation of mediastinal thymus III were found to be common on both sides of the neck and in both sexes. Parathyroid tissue was often associated or fused with thymic tissue. Investigators have found that cervical thymic tissue is so common in infants that it can be regarded as normal.[6,14] Only occasionally does cervical thymic tissue enlarge due to degeneration and hemorrhage or become cystic to present as a lateral neck mass. When it does, however, the mass may drain externally or (rarely) cause tracheal compression symptoms.[23]

Because of the important immunologic function of the thymus, it has been suggested that a cervical thymic mass in a child not be excised unless other functioning thymic tissue is present.[24] Since there are no radioactive markers for thymic tissue, x-ray films or tomograms in young children may reveal the presence of a mediastinal and/or cervical thymic shadow. There are reports of thymoma arising in solid cervical thymic tissue.[25]

Because of the report of neoplastic degeneration of cervical undescended thymus in the form of an epithelial thymoma[26] in an 11-year-old girl, the total removal of solid cervical thymic tissue has been suggested. However, there have been no reports of thymoma or malignant transformation in cystic cervical thymic tissue to date. Malignancy in ectopic thymic tissue has been reported.[14] In one case, clinical manifestations of myasthenia gravis have been attributed to a cervical low-midline benign thymoma.[27]

SUMMARY

The various types of cervical thymus may present as a neck mass, usually laterally, from the angle of the mandible to the manubrium. Since it is rare to diagnose the entity preoperatively, the differential diagnosis includes the more common branchial cleft cyst, thyroglossal duct cyst, cystic hygroma, cystic dermoid, and lesions of the salivary gland, thyroid, parathyroid, and cervical lymph nodes. Because cervical thymic tissue in various forms has been reported so frequently, we feel the entity should be considered in the clinical differential diagnosis of lateral neck mass, especially in the younger age group.

REFERENCES

1. Tori F, Mores A. The aberrant cervical thymus. Am J Surg 1978; 136:631-7.

2. Gilmour JR. The embryology of the parathyroid glands, the thymus, and certain associated rudiments. J Pathol Bacteriol 1937; 45:507-22.

3. Shier K. The morphology of the epithelial thymus. Lab Invest 1963; 12:316-26.

4. Patten BM. Human embryology. 3rd ed. New York: McGraw-Hill, 1968:431-42.

5. Weiss L, Greep RO. Histology. 4th ed. New York: McGraw-Hill, 1977:503-16.

6. Ellis HA, Knight B. Parathyroid and cervical thymus in sudden unexpected death in infancy. Pediatrics 1969; 44:225-33.

7. Speer F. Thymic cysts. Med Coll Flower Hosp Bull 1938; 1:142-50.

8. Ellis HA. Cervical thymic cysts. Br J Surg 1967; 54:17-20.

9. Willis RA. The borderland of embryology and pathology. 2nd ed. London: Butterworths, 1962:290-1.

10. Fielding JF, Farmer AW, Lindsay WK, Conen PE. Cystic degeneration in persistent cervical thymus. Can J Surg 1963; 6: 178-85.

11. Weller RW, Pearce A, Rappoport M. Thymic cyst of the neck. Arch Pathol 1951; 52:569-73.

12. Bieger RC, McAdams AJ. Thymic cysts. Arch Pathol 1966; 82:535-41.

13. Mikal S. Cervical thymic cyst. Arch Surg 1974; 109: 558-62.

14. Maisel H, Yoshihara H, Waggoner D. The cervical thymus. Mich Med 1975; 259-61.

15. Lewis MR. Persistence of the thymus in the cervical area. J Pediatr 1962; 61:887-93.

16. Sood VP, Chattopadhyay AK. Cervical thymic cyst. Eye Ear Nose Throat J 1976; 55:99-101.

17. Fahmy S. Cervical thymic cysts: their pathogenesis and relationship to branchial cysts. J Laryngol Otol 1974; 88:47-60.

18. Amr M. Cervical cysts, sinuses, and fistulae of branchial, pharyngothymic duct and thyroglossal duct origin. Br J Plast Surg 1964; 17:148-67.

19. Dzort J, Lejska V, Macik I. Cystis ductus thymopharyngei persistens. Cesk Otolaryngol 1979; 28:158-60.

20. Lydall D. Congenital cyst of third branchial cleft. Arch Otolaryngol 1956; 64:540-2.

21. Tucker HM, Skolnick ML. Fourth branchial cleft (pharyngeal pouch) remnant. Trans Am Acad Ophthalmol Otolaryngol 1973; 77:368-71.

22. Hagens EW. Malformation of the auditory apparatus in the newborn. Arch Otolaryngol 1932; 15:671-80.

23. McLeod D, Karandy E. Aberrant cervical thymus. Arch Otolaryngol 1981; 107:178-80.

24. Lewis CT. Ectopic thymus of the neck: report of three examples in children. Postgrad Med J 1975; 51:38-40.

25. Ridenhour CE, Henzel JH, deWeese MS, Kerr SE. Thymoma arising from undescended cervical thymus. Surgery 1970; 67 614-9.

26. Pirkey WP. Epithelioma of undescended thymus in a child. Arch Otolaryngol 1954; 59:237-40.

27. Sease CI. Cervical thymoma. Va Med Month 1956; 83:345-6.

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NINCDS NOTES*

NINCDS TRAINING SUPPORT REVEALED FOR FISCAL YEARS 1982 AND 1983

The NINCDS invested a total of $8.07 million in National Research Service Awards (NRSA) in fiscal year 1982, according to data recently compiled by the Institute. Of this sum, $3.79 million supported 2[illegible]9 individual postdoctoral fellowships; $4.31 million was designated for 288 trainees within 68 institutional training grants. The Institute also provided funds for 74 Research Career Development Awards (RCDAs), at $2.8 million. Teacher-Investigator Development Awards (TIDAs) in fiscal year 1982 supported another 106 individuals at a cost of $4.47 million.

Officials at NINCDS estimate that in fiscal year 1983, $9.7 million will be available for the postdoctoral fellowship and institutional training programs. Funding projections of $2.6 and $5.4 million have been made for RCDAs and TIDAs, respectively.

Individual NRSA postdoctoral fellowships support a specifically designated individual's further research training in the communicative sciences or neurosciences. Institutional NRSAs are granted to private or public organizations to provide similar research experiences for small groups of predoctoral and postdoctoral trainees.

Research Career Development Awards are designed for scientists with apparent research potential who are still in the formative stages of their careers. The RCDA provides a means by which these investigators gain additional experience in scientific environments conducive to the full development of research skills.

Teacher-Investigator Development Awards aim to recruit and prepare future teacher-investigators for careers in research and teaching in the neurological and communicative clinical disciplines, provide support for individuals with potential for research careers in an academic environment, and bridge the gap between the initial period of postdoctoral study and a secure academic appointment.

Eligibility information and application deadlines for these awards can be obtained from Dr. Donald H. Luecke, Deputy Director, Extramural Activities Program, NINCDS, Federal Building, Room 1016, 7550 Wisconsin Avenue, Bethesda MD 20205; (301) 496-4188.

NEW NINCDS FACT BOOK AVAILABLE

The *NINCDS Fact Book: July 1982*, a summary of the Institute's programs, personnel, and budget, is now available through the Office of Scientific and Health Reports. The 16-page publication, which includes information as recent as January 1983, outlines the Institute's organizational structure and lists department heads and key contacts in each program area. It also provides names and addresses of each of the Institute's advisory groups. Budget data include breakdowns of NINCDS research expenditures by disorder category as well as a budget history of the Institute and a look at the NINCDS budget as part of the NIH.

Single copies of the book can be obtained from the Office of Scientific and Health Reports, NINCDS, Bldg 31, Rm 8A08, 9000 Rockville Pike, Bethesda, MD 20205.

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*This information is prepared monthly by the Office of Scientific and Health Reports, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Building 31, Room A806, Bethesda MD 20205; (301) 496-5924.

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PRIMARY SQUAMOUS CELL CARCINOMA OF THE MIDDLE EAR INVADING THE COCHLEA

A HISTOPATHOLOGICAL CASE REPORT

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This report describes the histopathological changes in the temporal bone of a 71-year-old man who died of meningitis and epidural abscess complicated by primary squamous cell carcinoma of the middle ear. The present case is unusual and differs somewhat from previously reported cases of the primary squamous cell carcinoma of the middle ear in three respects: 1) an extensive invasion of the cancer into the membranous labyrinth, 2) cholesterol deposits in the cochlear spiral canal, and 3) presence of ossifying labyrinthitis. Among these findings, extensive involvement of the inner ear by cancer destroying the lower part of the otic capsule is particularly unusual. It is assumed that squamous cell carcinoma overcame the biological resistance to neoplastic infiltration which probably exists in the otic capsule and the membranous labyrinth.

INTRODUCTION

There are a few histopathological reports on temporal bones with primary carcinomas of the middle ear.[1-5] Recently we have had the opportunity to study the temporal bone of a patient who died of complications from the intracranial invasion of squamous cell carcinoma of the middle ear. The temporal bone histopathology in this case is worth reporting because of an unusual invasion of cancer cells into the membranous cochlea. The purpose of this paper is to document the histopathological findings in squamous cell carcinoma of the middle ear and to discuss its pathology in the inner ear.

CASE REPORT

The patient was a 71-year-old man who was admitted to Kikkoman Hospital with complaints of left aural discharge, facial nerve paralysis, and dizziness of several months' duration. Since the age of 30, acute exacerbations were treated as chronic otitis media by an otolaryngologist. On October 7, 1977, he was referred to the Department of Otolaryngology, National Defense Medical College, with the diagnosis of complications from chronic otitis media. Otological examination revealed a granulomatous mass filling the depths of the external auditory canal and the entire tympanic cavity. Within the granulomatous tissue, matrices of cholesteatoma were noted. The tympanic membrane could not be identified. Examination showed complete paralysis of the facial nerve. The patient had a profound hearing loss on the affected side. Mastoid x-ray films demonstrated extensive destruction of the left petrous bone. On November 14, 1977, a radical mastoidectomy was performed. The middle ear cavity was almost entirely replaced by tumorous tissue and matrices of cholesteatoma. There was a large bony defect in the tegmen of the tympanic cavity where dura was exposed. As much of the pathological tissue as possible was removed. Histopathological examination revealed well-differentiated squamous cell carcinoma accompanied by cholesteatoma. The patient suffered a progressive downhill course after ear surgery. Clinical signs of meningitis were noted on the fifth postoperative day. Approximately 1 month later, the patient died of meningitis and an epidural abscess. Because of his critical condition no antitumorous therapy such as irradiation and/or systemic chemotherapy was administered. An autopsy was performed three hours after death. At autopsy, an extensive invasion of the tumor was noted from the middle ear to the middle and posterior cranial fossae. Meningeal infiltration by the tumor cells was also noted, especially over the cerebellum. The brain was markedly edematous and softened. No distant metastases were found. The left temporal bone was removed four hours postmortem for histopathological study. The bone was fixed in 10% formalin and processed by the conventional celloidin method. The bone was cut horizontally at a 20-μ thickness and every tenth section was stained with hematoxylin and eosin and examined by light microscopy.

Histopathology of the Temporal Bone. Extensive neoplastic involvement of the petrous portion of the temporal bone was found. The internal auditory

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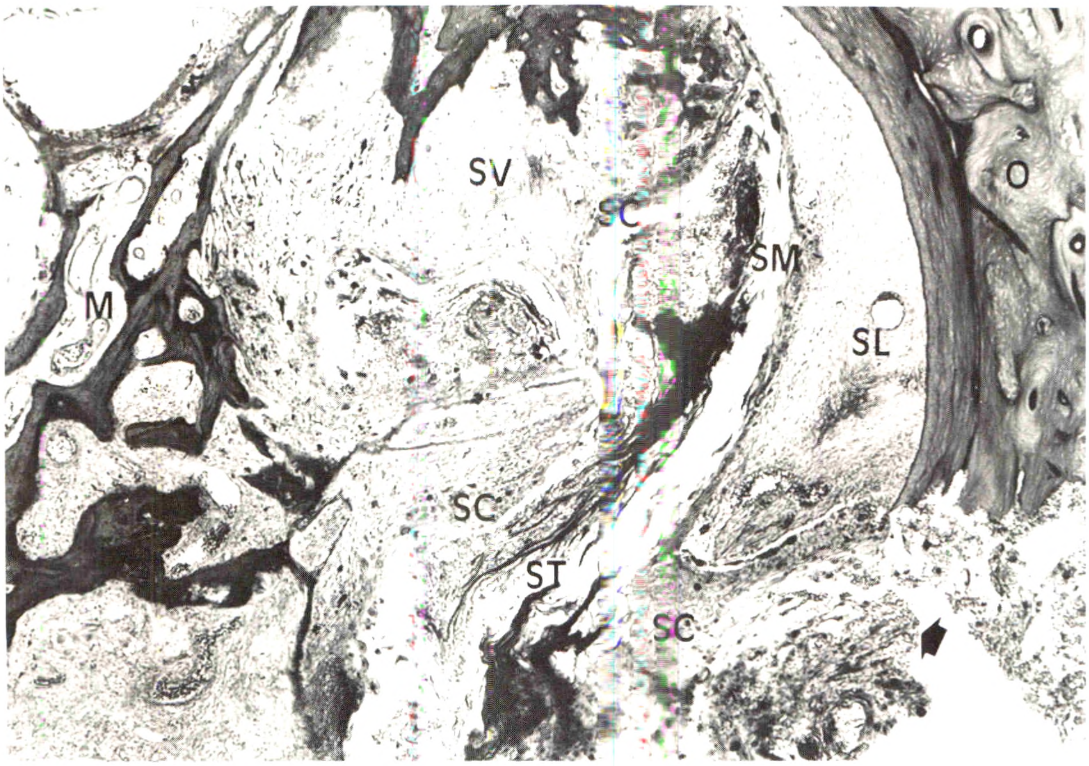

Fig 1. Tumor tissue (SC) mainly in scala tympani (ST) of basal turn. It extends into scala media (SM) and to scala vestibuli (SV) by destroying basilar membrane and Reissner's membrane. Arrow indicates invasion route from middle ear to membranous cochlea. M - Modiolus; O - Otic capsule; SL - Spiral ligament. (x60)

canal, including both the seventh and eighth nerves, was infiltrated by cancer cells. Most fibers in both nerves were atrophic. A few Scarpa's ganglion cells were identified. The postoperative cavity of the tympanum, antrum, and mastoid was filled with clusters of neoplastic cells, necrotic material, and inflammatory tissue. The matrices of cholesteatoma could not be found. All the bones composing the middle ear cavity were more or less eroded by the cancer. The horizontal portion of the fallopian canal had no bony wall. The facial nerve was partly replaced by malignant tumor cells. The number of the facial nerve fibers was markedly reduced in this region. The tumor invasion in the facial nerve was less severe in the peripheral part of the nerve. The tympanic membrane, malleus, and incus were absent, either because of the previous ear operation or as a result of destruction by the tumor. The stapes and most of the vestibule could not be identified because they were not included in the series of stained sections. There were clusters of tumor cells in the tympanic orifice of the eustachian tube, almost occluding its lumen. The wall of the external auditory canal was partly destroyed by the tumor. Varying degrees of erosion of the bony labyrinth were observed. Squamous cell carcinoma invaded the membranous cochlea, especially in the basal turn through the inferior part of the bony cochlea. The whole cochlear spiral canal of the basal turn was occupied by neoplastic, fibrous and osseous tissues, the latter of which was the result of labyrinthitis. Tumorous tissue was noted mainly in the scala tympani of the basal turn. It extended to the scala media and to the scala vestibuli by destroying the basilar membrane and Reissner's membrane (Fig 1). The interscalar septae were normal. New bone formation was noted in scala vestibuli adjacent to the interscalar septum of the basal turn. Reissner's membrane could not be identified. In both perilymphatic and endolymphatic spaces, the tumor cells had characteristic features of squamous cell carcinoma and they showed varying degrees of differentiation. Most of them were relatively well differentiated. Extensive keratinization was found on the surface of the tumor-cell lining (Fig 2). Some malignant cells were seen floating with inflammatory cells in the spaces of the cochlear spiral canal. Most of the cells composing the organ of Corti of the basal turn were missing because of the extensive destruction of the membranous labyrinth by the neoplastic growth and the secondary labyrinthitis. The stria vascularis was replaced by the tumor cells. In the modiolus, most of the nerve fibers were atrophied and the majority of spiral ganglion cells were missing (Fig 3). A considerable degree of ossification was noted in the modiolus, especially in the perineural and perivascular spaces. The structures of the membranous labyrinth of the middle and apical turns were deformed by the inflammation. Some evidence of acute inflammation was found. The lymphatic spaces contained a considerable amount of acidophilic fluid. Areas of

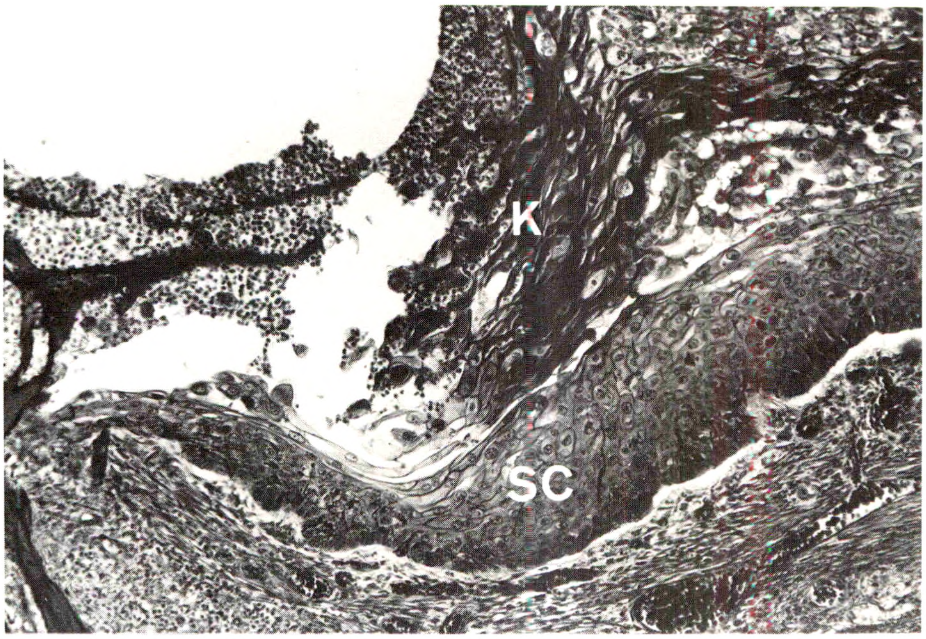

Fig 2. Extensive keratinization (K) on surface of tumor cells (SC). (x150)

hemorrhage were noted in the spiral canal of the apical turn. In the vicinity of old hemorrhages, cholesterol clefts accompanied by foam cells, hemosiderin pigment cells, and some inflammatory cells were visible (Fig 4). No neoplastic cells were found in the spiral canal of the middle and apical turns of the cochlea. The petrous apex was normal and contained bone marrow. The carotid artery was normal.

DISCUSSION

The present case is uncommon and differs somewhat from previously reported cases of primary squamous cell carcinoma of the middle ear in three respects: 1) an extensive invasion of the cancer into the membranous labyrinth; 2) cholesterol deposits in the cochlear spiral canal; and 3) presence of ossifying labyrinthitis.

There are several histopathological studies of squamous cell carcinoma of the middle ear.[1-6] However, in only a few cases was there extension into the inner ear. Rosenwasser's case[1] is the only one which showed an invasion of primary squamous cell carcinoma of the middle ear into the membranous cochlea by direct destruction of the otic capsule. Schuknecht[3] described a case of primary squamous cell carcinoma of the middle ear invading Rosenthal's canal, the modiolus, the scala tympani, and the scala vestibuli. However, the route of invasion was not mentioned.

Although metastatic lesions usually resemble primary tumors in histological appearance, they are often less well differentiated. Accordingly, the behavior of a metastatic tumor might differ from that of a primary one. It is well known that metastases occur more rapidly or easily with sarcomas than

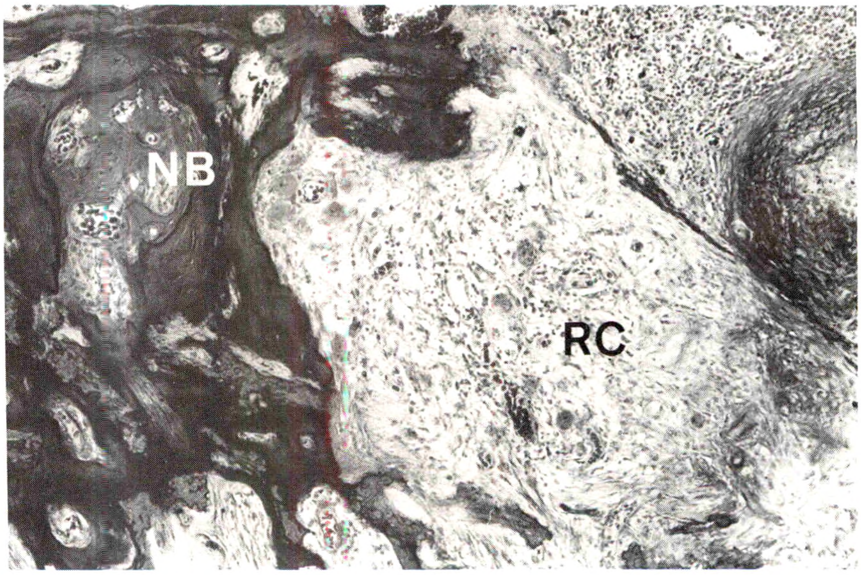

Fig 3. Rosenthal's canal (RC) showing few spiral ganglion cells. NB - New bone. (x150)

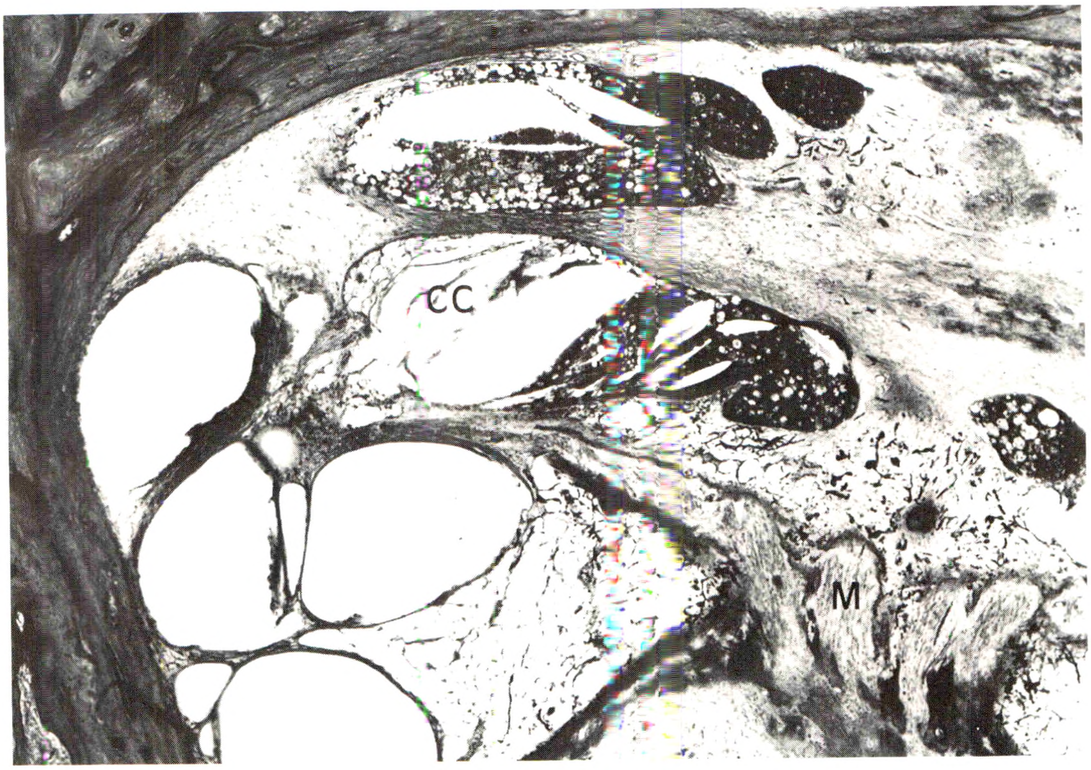

Fig 4. Cholesterol clefts (CC) in acidophilic fluids in lymphatic spaces of upper turns. M - Modiolus. (x60)

carcinomas. On the other hand, several histopathological studies of the temporal bone indicated that sarcomas show much more extensive inner ear invasion than carcinomas, even in cases of metastatic tumors.[7,8] Primary sarcoma of the middle ear usually does not invade directly into the inner ear by destroying the bony labyrinth. After filling the epitympanum, it extends first into the internal auditory canal through the genu along the facial nerve, then invades retrogradely the basal turn of the cochlea and the vestibule through the cribriform areas of the fundus of the internal auditory canal. El-Gathamy et al[7] described a case in which a rhabdomyosarcoma originating from the anterior part of the middle ear extended to the attic, then into the internal auditory canal. From the internal auditory canal, sarcoma cells invaded retrogradely into the basal turn of the cochlea and the utricular portion of the vestibule. Primary osteogenic sarcoma of the middle ear reported by Naufal[8] showed almost the same behavior as the rhabdomyosarcoma described above. Thus, invasion through the internal auditory canal is the most common route for inner ear involvement with either primary or metastatic tumors of the temporal bone.

In the cochlea, most of these malignancies reveal tumor cell infiltration from the internal auditory canal to Rosenthal's canal or as far as the proximal half of the osseous spiral lamina. Hoshino et al[9] reported a case with inner ear involvement with a papillary adenocarcinoma metastatic from the lung. Tumor cells infiltrated into the modiolus along the cochlear nerve fibers. They were also seen in Rosenthal's canal along its entire length except for the most apical region. Distal to Rosenthal's canal, tumor cells extended into the osseous spiral lamina up to the habenula perforata in the hook portion, lower basal turn and anterior half of the upper basal turn. It is well known that among carcinomas, adenocarcinoma has a tendency to extend farther peripherally along the nerve fibers. Meller[10] suggested that some biological resistance may exist at the osseous spiral lamina, the cribriform areas of the fundus of the internal auditory canal, and the geniculate ganglion, because in most cases, the invasion of the tumor cells ends at the aforementioned sites. The tendency of the tumor to invade the inner ear by this route usually depends on the duration of the clinical course and nature of the tumor.

Direct invasion by destruction of the otic capsule is another route whereby the inner ear can be involved by a malignancy in the middle ear. Adams et al[2] reported that, although the otic capsule of six patients with secondary malignancies of the temporal bone was invaded by tumor, in no case did it extend through the endosteal layer. This is a characteristic finding in malignancies of the temporal bone. Schuknecht et al[6] stressed that the otic capsule and the membranous labyrinth are quite resistant to neoplasm. In the present case, however, the cancer destroyed the lower part of the otic capsule and invaded the inner ear. Evidently the tumor cells overcame the biological resistance to neoplastic infiltration which probably exists in the otic capsule and membranous labyrinth.

Malignant tumors of the temporal bone sometimes induce cochlear and vestibular dysfunctions and facial nerve paralysis.[3,4,11,12] In the present case, audiograms showed a profound hearing loss in the affected ear. The hearing loss was the result of 1) destruction of cochlear nerve fibers, 2) compression of the fibers in the internal auditory canal, 3) destruction of the membranous labyrinth, or 4) secondary labyrinthitis. Left facial nerve paralysis was one of the chief complaints in the present case. The histological sections revealed that the facial nerve was destroyed by the neoplasm, especially in the internal auditory canal and tympanic portion.

Cholesterol formation was found in the acidophilic fluids of the apical spiral canal of the cochlea. Cholesterol crystals were observed frequently in the vicinity of the hemorrhages and may have been formed from serum cholesterol that leaked out from blood vessels. The hemorrhages in the membranous labyrinth probably occur in the congested soft tissues as a result of secondary inflammatory response. Friedmann[4] observed cholesterol crystals in the scala tympani and the scala vestibuli in a case of metastatic bronchial carcinoma invading the temporal bone.

Squamous cell carcinoma and cholesteatoma coexisted in the middle ear of the present case. Several other investigators have reported similar findings.[4,13] It is possible that chronic otitis media and its complications such as epidermoid cholesteatoma may be predisposing factors of primary squamous cell carcinoma of the middle ear.[4] Boland and Paterson[14] found an obvious association of pre-existing infections of the middle ear cavity with the subsequent development of carcinoma.

Labyrinthitis usually occurs in the spiral canal of the cochlea which has been invaded by a malignancy, especially by primary middle ear tumor. Secondary suppurative labyrinthitis is generally caused by chronic otitis media which occurs frequently in the middle ears with the malignant tumor.

Paparella and Sugiura[15] divided the pathology of suppurative labyrinthitis into three stages: acute, fibrous and ossification. Depending upon the site and severity of the inflammatory process, these stages often overlap one another. In general, however, the acute stage precedes the fibrous stage which then develops into the ossification stage. Pathological changes of the acute stage and fibrous stage are often seen concurrently, whereas the fibrous stage and ossification stage are usually present together. The present case showed labyrinthitis of both the fibrous and ossification stages. New bone formation was also present in the spiral canal of the basal turn. New bone is considered to be characteristic of the terminal stage of the repair process. Druss[16] believed the new bone formation to be of two types, metaplastic and osteoplastic. According to his interpretation, the metaplastic type of bone originates from the scar or connective tissue within the inner ear and the osteoplastic type originates from the adjacent bony capsule which is exposed by virtue of destruction of its endosteal lining. The present case was seemingly of metaplastic type because the endosteal bone lining the labyrinthine space adjacent to the new bone was intact and no continuation of bony tissues was found between them.

Involvement of the membranous cochlea by primary malignancy of the middle ear has rarely been reported in the literature. Further histological investigations of this kind of lesion will clarify whether or not the biological resistance to neoplastic infiltration is present in the otic capsule and the membranous labyrinth.

REFERENCES

1. Rosenwasser H. Neoplasms involving the middle ear. Arch Otolaryngol 1940; 32:38-53.

2. Adams GL, Paparella MM, El Fiky FM. Primary and metastatic tumors of the temporal bone. Laryngoscope 1971; 81: 1273-85.

3. Schuknecht HF. Pathology of the ear. Boston: Harvard University Press, 1974.

4. Friedmann I. Pathology of the ear. Oxford: Blackwell Scientific Publications, 1974.

5. Wagenfeld DJH, Keane T, van Nostrand AWP, Bryce DP. Primary carcinoma involving the temporal bone: analysis of twenty-five cases. Laryngoscope 1980; 90:912-9.

6. Schuknecht HF, Allam AF, Murakami Y. Pathology of secondary malignant tumors of the temporal bone. Ann Otol Rhinol Laryngol 1968; 77:5-22.

7. El-Gathamy B, Fujita S, Hayden RC. Rhabdomyosarcoma — a temporal bone report. Arch Otolaryngol 1973; 98: 106-10.

8. Naufal PM. Primary sarcomas of the temporal bone. Arch Otolaryngol 1973; 98:44-50.

9. Hoshino T, Hiraide F, Nomura Y. Metastatic tumor of the inner ear: a histopathological report. J Laryngol Otol 1972; 86: 697-707.

10. Meller H. Zur Frage der Meningitis carcinomatosa des Schlafenbeines. Wien Klin Wochenschr 1939; 52:114-7.

11. Nakai Y, Yamazaki T, Yamamoto K, Hakuba A. Inner ear pathology in middle ear cancer. Clin Otol Jap 1976; 3:24-5.

12. Bergstrom L, Baker BB, Sando I. Sudden deafness and facial palsy from metastatic bronchogenic carcinoma. J Laryngol Otol 1977; 91:787-93.

13. Coachman EH. Squamous cell carcinoma secondary to cholesteatoma. Arch Otolaryngol 1951; 54:187.

14. Boland J, Paterson R. Cancer of the middle ear and external auditory meatus. J Laryngol Otol 1955; 69:468-78.

15. Paparella MM, Sugiura S. The pathology of suppurative labyrinthitis. Ann Otol Rhinol Laryngol 1967; 76:554-86.

16. Druss J. Labyrinthitis secondary to meningococcic meningitis. A clinical and histopathological study. Arch Otolaryngol 1936; 24:19-28.

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SECRETORY IMMUNE RESPONSE IN PATIENTS WITH OROPHARYNGEAL CARCINOMA

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The secretory immune system is a unique, local immunological mechanism which appears to be independent of systemic immunity. Secretory immunoglobulin A (SIgA), a major component in this mucosal immune system, is structurally different from the IgA immunoglobulin in serum and has a function as a first line of defense against the uptake of macromolecules and against infectious agents in the intestine, respiratory tract and genitourinary system. However, its relationship to the development and control of neoplasia is not well understood despite the fact that the major portion of human malignancies are of the epithelial type and located where the secretory immune system is vigorously functioning. In this study, the amounts of SIgA and secretory component (SC) in oral secretions and sera were measured in 20 patients with oropharyngeal carcinoma and 22 appropriate control subjects in order to elucidate the involvement of the secretory immune system as it related to oropharyngeal carcinoma. Cancer patients had increased IgA levels in oral secretions (561 ± 161 μg/ml) compared to normal subjects (166 ± 18 μg/ml, $p<0.02$) and to a smoker/drinker subgroup of controls (229 ± 8.7 μg/ml, $p<0.05$). The elevated IgA levels in cancer patients appear to be unrelated to local inflammation or the patient's history of smoking or drinking. Density gradient analysis demonstrated that the IgA measured in oral secretions migrates at the 11S position, confirming that it is of the secretory type and indicating that the increased levels of IgA in oral secretions of patients with oropharyngeal carcinoma are not due to nonspecific leakage of 7 SIgA from sera. Secretory component levels in sera also revealed highly significant differences between cancer patients (1.65 ± 0.73 μg/ml) and all control subjects (0.85 ± 0.12 μg/ml, $p<0.002$). The data suggest that the increased SIgA concentration in secretions and SC level in sera accompany the existence of oropharyngeal carcinoma. The biological significance of these findings and their possible clinical application are discussed.

The secretory immune system is important as a first line of defense against the penetration of the epithelial surface by a variety of pathologic organisms and macromolecules. Secretory IgA (SIgA) exists in virtually any external secretion on mucosal surfaces such as the oropharynx, nasal cavity, intestine and genitourinary tract[1] and possesses specific antiviral and antibacterial function. It also appears to have a role in interfering with the uptake of macromoleucles which exist in food. However the nature of its relationship to various forms of neoplasia is not well understood.

IgA is a major product of the local secretory immune system and is present in nearly all mucosal surfaces. Its structure is more complex than the IgA of serum. SIgA consists of three immunologically distinct components: 1) 10S dimer of IgA, 2) a joining piece (J-chain), and 3) secretory component (SC). Monomeric 7S IgA, and J-chain are produced by the plasma cells located in submucosa and two molecules of IgA are bound with a J-chain to produce 10S dimeric IgA. Secretory component, produced by the epithelial cell, is then attached to the dimeric IgA by covalent as well as noncovalent bonds. Binding of SC appears to protect dimeric IgA from the action of proteolytic enzymes, such as trypsin, chymotrypsin and pepsin, frequently located in mucous media where this immunoglobulin fulfills its biological action.[1] Normally there are only minimal amounts of SIgA in serum.[2]

Most human malignancies are of epithelial derivation and occur in regions where the secretory immune system is functioning. In this study, the amounts of SIgA and SC in oral secretions and sera as well as serum IgA and IgG were measured in order to elucidate the possible involvement of the secretory immune system in patients with oropharyngeal carcinoma.

METHODS

Patient Population. A total of 42 subjects were studied at Duke University Medical Center and the Durham VA Medical Center. The Table stratifies the patients studied; 20 exhibited oropharyngeal carcinoma and 22 were control subjects. Sites of orpharyngeal carcinoma were tonsil (three patients), tongue (six patients), floor of mouth (seven patients), palate (two patients) and hypopharynx (two patients). The control subjects were subgrouped into three categories: eight healthy volunteers, nine in a smoker/drinker subgroup, and five patients with various otolaryngological disorders (chronic sinusitis, allergic rhinosinusitis, chronic otitis media, hemangioma of oropharynx, severe periodontal disease). Diagnosis of oropharyngeal carcinoma was confirmed by pathological examination of biopsy materials or surgical specimens and interpreted as squamous cell carcinoma. Staging was determined at the initial clinical examination according to criteria of the American Joint Committee for Cancer Staging and the End-Result Reporting.[3] Smoker/drinker groups are defined as containing those patients with 1) a smoking history of over three years within a ten-year period prior to entry into this study,

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STRATIFICATION OF PATIENTS STUDIED

Groups of Patients	*No. of Patients*	*Age*
Oropharyngeal carcinoma		62 ± 11
Stage I	2	
II	8	
III	5	
IV	5	
Total	20	
Control subjects		
Normal	8	49 ± 9
Smoker/drinker	9	49 ± 12
Other ENT pathology	5	42 ± 10
Total	22	

and/or 2) a history of alcohol consumption for which the patient was or has been referred to the medical or psychiatric services at our institutions during the similar time frame. Other otolaryngological disorders were diagnosed by ordinary medical criteria and represented cases without prior history of malignant disease. Normal volunteers represented individuals without a history of other systemic diseases and were not smokers or drinkers. None of the subjects of this study had renal insufficiency or hepatic damage as evidenced by the values of serum electrolytes, BUN, albumin, total and direct bilirubin, SGOT and alkaline phosphatase.

Salivary and Serum Samples. In order to obtain salivary samples avoiding the effects of food intake and diurnal change of salivary production, two salivary samples were obtained from each subject. The first sample, designated as an oral secretion, was obtained in midmorning by expectoration for 15 minutes after having the subject rinse the oral cavity with sterile saline solution. A second sample, designated as an oral washing, was obtained by having the subject rinse the oropharynx with 15 ml of sterile normal saline. A blood sample was obtained at the same time by venipuncture, coagulated at room temperature, and the serum removed for analysis.

Immunological Assays and Sucrose Gradient Ultracentrifugation. IgA in oral secretions, oral washings, as well as SC in serum were measured by competition radioimmunoassays (RIA) utilizing rabbit antiserum against the α-chain of human serum IgA or rabbit antiserum against human SC (Calbiochem-Behring Corp, La Jolla, Cal). Iodine 125-radiolabeled human secretory (11S) IgA or SC, which were purified from human colostrum,[1-4] were used as competing antigens. Other proteins abundant in secretion (albumin, transferrin, IgG) did not compete in these assays.[5] Sucrose density analysis was performed on oral secretions according to standard techniques[6] in order to separate 7S and 11S IgA and to determine the distribution of SC. The positions in the gradient of the IgA and SC were determined by RIA and compared to the migration of a 7S marker (radiolabeled-human IgG, Cappel Labs, Cochranville, Pa) and an 11S marker (Catalase, Worthington Biochemical Corp, Freehold, NJ). Serum IgA and IgG were measured by using commercially available quantitative radioimmunodiffusion (RID) plates (Meloy Labs, Springfield, Va). Results of IgA, IgG and SC were expressed as mean ± 1 standard deviation and the nonparametric Mann-Whitney U-Test was used for statistical analyses.

RESULTS

Oral Secretion. IgA concentration in oral secretions from patients with oropharyngeal carcinoma was 571 ± 169 μg/ml. This was significantly higher than that of normal volunteers (166 ± 18 μg/ml, $p < 0.002$), or of the smoker/drinker group (229 ± 7 μg/ml, $p < 0.05$), but not statistically significant when compared with the other ENT pathology group (358 ± 274 μg/ml, $p = 0.1$). Since the total volume of oral secretions had a wide range of variety among subjects (1.3 to 25.4 ml/15 min), the IgA value was standardized by multiplying the level obtained by the volume collected in 15 minutes. In Figure 1, each dot represents an individual determination of 15 minute-timed IgA in the oral secretion. Values obtained in this fashion demonstrated more striking statistically significant differences between cancer patients and normal volunteers ($p < 0.03$), the smoker/drinker group ($p < 0.002$), and the other ENT pathology group ($p < 0.05$).

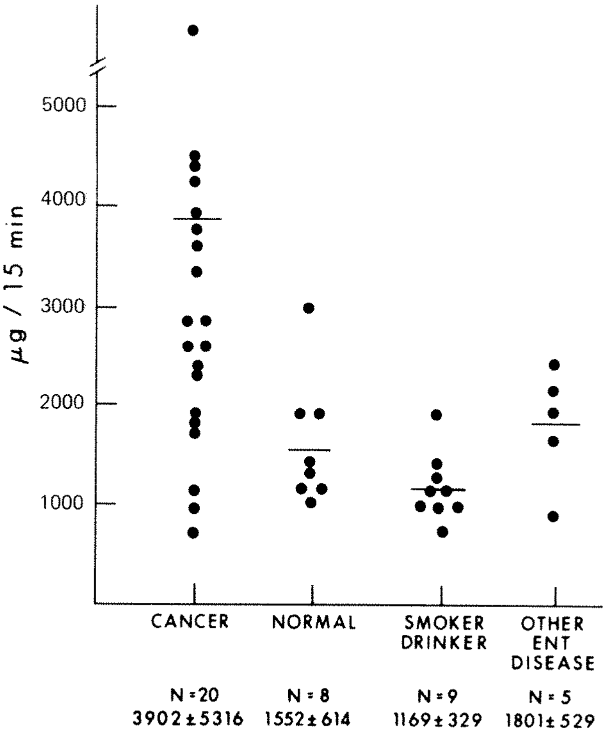

Fig 1. Fifteen minute-timed total IgA levels in oral secretions. Values were calculated by multiplying IgA value in oral secretion by volume of oral secretion obtained in a 15-minute period. Mean value for each group is indicated by small horizontal bars.

Oral Washing. The oral washing sample was obtained by having the patient rinse the oropharynx with 15 ml of normal saline at the completion of saliva expectoration. IgA concentration in the oral washings showed even more impressive discriminating potentials among the groups as demonstrated by Figure 2. The values obtained were below 1 μg/ml in normal volunteer subjects but above 1 μg/ml in all samples obtained from 19 cancer patients, the smoker/drinker group, and patients with other otolaryngologic disorders. The IgA level in washing samples from patients with oropharyngeal carcinoma was 22.2 ± 5.7 μg/ml and significantly higher than that of the normal volunteer group (0.08 ± 0.1 μg/ml, $p < 0.005$), the smoker/drinker group (6.7 ± 0.9 μg/ml, $p < 0.005$) and other ENT pathology groups (8.8 ± 3.1 μg/ml, $p < 0.005$). The IgA level in washing samples from the normal volunteers was lower than that of the smoker/drinker group ($p < 0.01$) and the other ENT pathology group ($p < 0.01$). However, there was no significant

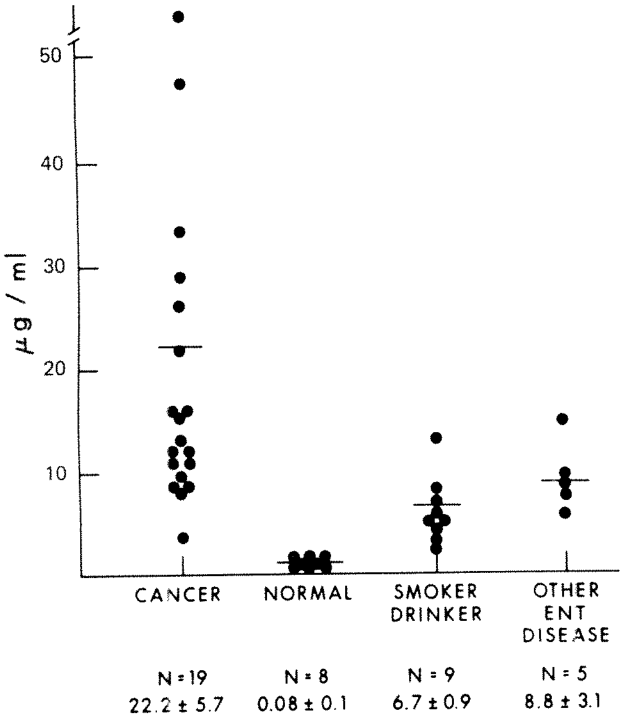

Fig 2. IgA levels in oral washings. Oral washings were obtained after 15 minutes of saliva expectoration and represent de novo IgA production. Values obtained showed high discrimination between cancer patients and other control subjects.

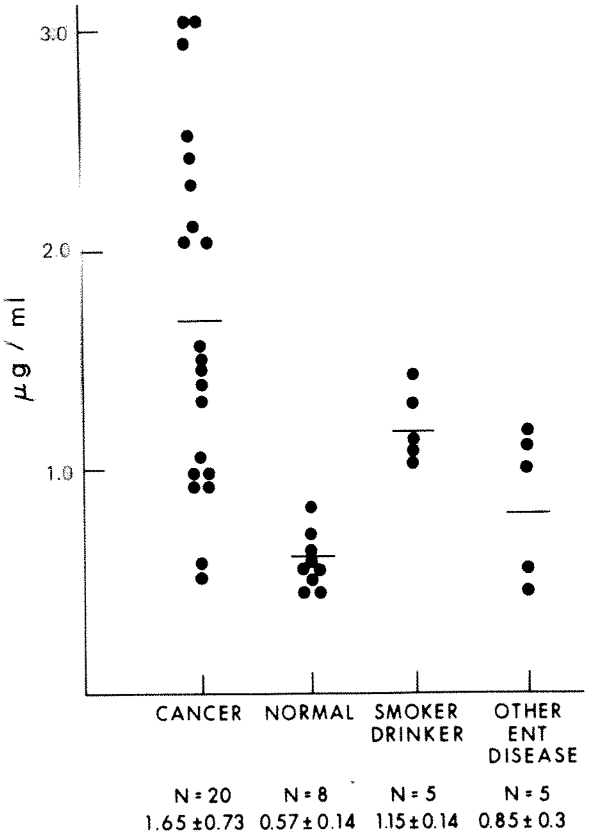

Fig 3. Levels of secretory component in serum.

difference between the smoker/drinker group and the other ENT pathology group ($p > 0.1$).

IgA levels in oral washings showed the highest discrimination among these groups of any measurement obtained in this study.

Serum IgA and IgG. Serum IgA, which is virtually all in 7S monomer form, and serum IgG were measured by RID. The cancer-patient group had a significantly higher level of serum IgA (3.4 ± 0.2 mg/ml) compared to the normal volunteers (1.9 ± 0.1 mg/ml), the smoker/drinker group (2.1 ± 0.2 mg/ml) and the other ENT pathology group (2.0 ± 0.1 mg/ml, $p < 0.005$, respectively). There was no difference of serum IgG level among these groups.

Secretory Component Level in Serum. The SC level in serum was also measured by a specific competition RIA (Fig 3). Mean SC levels in sera from patients with oropharyngeal carcinoma were 1.65 ± 0.73 μg/ml and this was significantly higher than that of the normal volunteers ($p < 0.002$), but not statistically significant when compared to the smoker/drinker group ($p = 0.1$) or the other ENT pathology group ($p = 0.1$).

Immunochemical Characteristics of IgA in Oral Secretion. The characteristics of the IgA in oral secretions were evaluated through sedimentation in a sucrose gradient. This was performed on three normal, three cancer, two smoker/drinker and two other ENT pathology subjects. Figure 4 demonstrates the results from one oral secretion from the patients with tongue carcinoma.

IgA and SC were determined by respective competition RIA throughout the gradient and their relative sedimentation was determined by comparison to radiolabeled 7S (IgA) and 11S (catalase) markers (right-side ordinate). The IgA activity peaked at 11S, indicating that it was in the form of secretory IgA. Secretory component activity was found mainly in free form at the 4.2S position and a small peak at 11S indicating SC attached to secretory IgA. All gradients examined showed the same pattern regardless of pathology.

IgA observed in secretions was essentially all SIgA and this suggests that the SIgA was specifically and actively transported by the secretory immune system and not merely a reflection of increased transudation of 7SIgA from serum, which contains 7-to-12-fold more IgA compared to oral secretions.

TNM Stage and IgA Levels. Elevated levels of IgA observed in both serum and oral secretions from patients with oropharyngeal carcinoma did not reflect the TNM stage in this study. In other words, the increase of IgA does not correlate with the stage of the cancer. Nodal involvement did not influence the level of IgA in secretion and serum. However, further study is necessary since the patient population was too small to determine statistical significance.

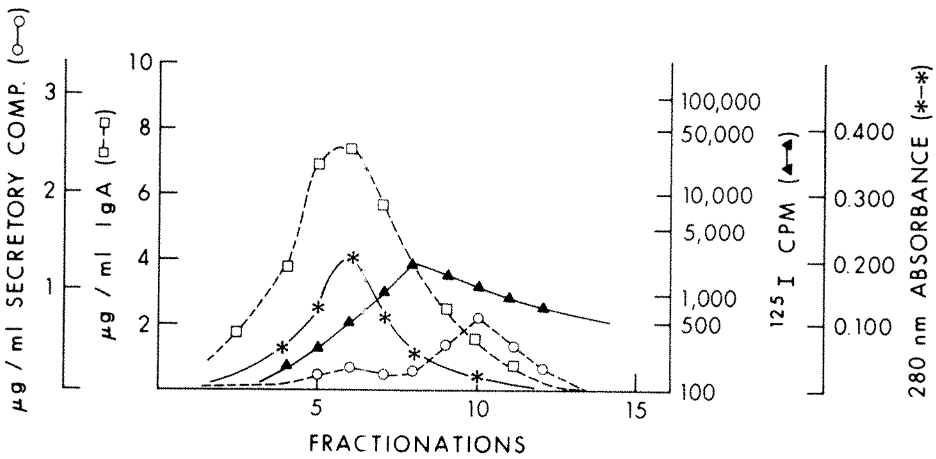

Fig 4. Density gradient ultracentrifugation of oral secretion sample from patient with tongue carcinoma (T_3N_0). IgA peak is located at 11S position (same as 11S catalase marker). Secretory component was found predominantly at 4.2S with a minor amount at 11S position, suggesting an association with IgA. □ - IgA in oral secretion by RIA; ○ - Secretory component by RIA; * - Catalase (11S) by 280-nm absorbance; ▲ - Iodine 125-labeled human IgG (7S).

Effects of Smoking/Drinking and Local Infection. One consideration during the study was to obtain the detailed clinical history of smoking and drinking. It is well documented that cancer of the oropharynx is associated with heavy alcohol consumption and smoking.[7] We wished to determine whether smoking and alcohol consumption affect the level of IgA in oral secretions. Seventeen patients with oropharyngeal carcinoma (85%) were heavy alcohol and tobacco users; however, three patients who had elevated IgA levels in oral secretions (358, 358, 337 µg/ml, respectively) did not have histories of any use of alcohol or tobacco. This supports the hypothesis that the elevated levels of IgA in oral secretions are not simply induced through mucosal irritation by alcohol or inhalation of smoke. Another consideration was the effect of local inflammation in the oropharynx on the levels of IgA. Other otolaryngological disorders which involved various mucous surfaces in the head and neck region showed variable levels of IgA in oral secretions (122 to 710 µg/ml), although their 15 minute-timed IgA showed only a small variation in the group (Fig 1). Furthermore, four of nine subjects in the smoker/drinker subgroup had moderate to severe periodontal disease and their IgA level in oral secretions and washings was lower than the average of the group of other ENT pathologies. This suggests that the inflammatory process itself does not increase the amount of IgA.

It is conceivable that the neoplastic tissue in the oropharynx might be heavily infected with bacterium and result in the stimulation of large amounts of immunoglobulins. However, oral secretions from patients with oropharyngeal carcinoma did not contain significant amounts of albumin or IgG (data not shown), which is known to dramatically increase in secretions associated with inflammatory processes.[1] This further suggests that the elevated IgA level in oral secretions has an apparent association with oropharyngeal carcinoma.

DISCUSSION

The data presented in this study further support and extend previous reports[8] that oropharyngeal carcinoma is associated with high levels of IgA in secretions bathing the neoplasm. This was confirmed by sensitive RIA rather than immunodiffusion techniques which were used in previous studies.[8,9] Furthermore the method of sample collection, namely midmorning oral washings with saline, resulted in uniform samples containing de novo secretions of IgA rather than accumulated IgA in the oropharynx.

The sucrose gradient fractionation demonstrated that the elevated IgA in oral secretions was in the 11S form, indicating that its derivation was from specific transport by the secretory immune system rather than increased transudation from serum, which contains 7-to-12-fold more IgA compared to oral secretions.[1] Recent studies with bronchial lavage from patients with bronchogenic carcinoma and gastric aspirates from patients with carcinoma of the stomach revealed similar findings[5,9,10] and reflect the involvement of the local secretory immune system with the neoplastic process. Considered together with our results, the elevated IgA level in external secretions may reflect an underlying immune response to, as yet, unidentified antigen(s) associated with epithelial malignancies.

The patients with oropharyngeal carcinoma also exhibited elevated levels of SC in serum. It is known that several types of epithelial tumors such as ovarian carcinoma, breast carcinoma, and nasopharyngeal carcinoma secrete this material.[11-13] The elevated SC in serum observed in this study may originate from the neoplastic tissue itself and become absorbed via the lymphatics into the serum either in free form or bound to IgA. We also observed elevated IgA levels in serum from cancer patients, which is in accord with previous studies on head and neck cancers as well as other epithelial malignancies.[14] However, there are no significant correlations between the high levels of IgA in secretions and levels of IgA or SC in serum in the cancer-patient group.

Involvement of the secretory immune system in head and neck carcinoma is not only biologically interesting but may also be of clinical value. Brown et al[8] reported that the IgA level in whole saliva correlated with tumor load of oropharyngeal carcinoma. In their study, the IgA level in oral secretions was significantly decreased after the successful treatment. It has also been reported that the elevated IgA in serum from patients with head and neck malignancies correlated with poor prognosis.[14,15] In our study, SIgA determination had remarkable discriminating function between cancer patients and control subjects. The elevated level of SC in serum might also be an indicator of tumor load. This determination has the advantage that dilutional problems inherent to the collecting secretory fluid can be avoided. Measurements of SIgA in oral secretions and SC in serum may thus serve as tumor markers for oropharyngeal carcinoma and as a supplemental diagnostic armamentarium in the follow-up care of head and neck cancer patients. These questions along with the biological and immunological significance of the increased secretion of these materials in association with epithelial malignancies are currently under study.

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REFERENCES

1. Tomasi TB. The immune system of secretions. Englewood Cliffs, NJ: Prentice-Hall, 1976.

2. Waldman RH, Mach JP, Stella MM, Rowe DS. Secretory IgA in human serum. J Immunol 1970; 105:43-7.

3. American Joint Committee for Cancer Staging and the End-Result Reporting, Chicago, 1978.

4. Heide K, Schwick HG. Salt fractionation of immunoglobulins. In: Weir DM, ed. Handbook of experimental immunology. Vol 1. Immunochemistry. Oxford: Blackwell Scientific Publications, 1978:7.1-7.11.

5. Iglehart JD, Warzynski MJS, Montelaro RC, Bolognesi DP, Sabiston DC Jr, Wolfe WG. Function of the secretory immune system in bronchogenic carcinoma. J Thorac Cardiovasc Surg 1981; 82:63-9.

6. Tomasi TB, Tan EM, Soloman A, Prendergast RA. Characteristics of an immune system common to certain external secretions. J Exp Med 1965; 121:101-24.

7. Keller AZ. Cirrhosis of the liver, alcoholism and heavy smoking associated with cancer of the mouth and pharynx. Cancer 1967; 20:1015-22.

8. Brown AM, Lally ET, Frankel A, Harwick R, Davis LW, Rominger CJ. The association of the IgA level of serum and whole saliva with the progression of oral cancer. Cancer 1975; 35: 1154-62.

9. Mandel MA, Evorak KJ, Workman LW, DeCosse JJ. Immunoglobulin content in the bronchial washings of patients with benign and malignant pulmonary disease. N Engl J Med 1976; 295:694-8.

10. Levy M, Petreshock EP, Mandell C, Deysine M, Katzka I, Aufses AH Jr. The response of the local immunoglobulin system to malignant lesion of the stomach. Cancer 1975; 35:1991-5.

11. Harris JP, Caleb MH, South MA. Secretory component in human mammary carcinoma. Cancer Res 1975; 35:1861-4.

12. Desgranges C, Li JY, De-The G. EBV specific secretory IgA in saliva of NPC patients. Presence of secretory piece in epithelial malignant cells. Int J Cancer 1977; 20:881-6.

13. Garcia JA, Klein JL, Kutteh WH, Dawson JR, Gall SA. Immunologic studies on the cystic effusion of ovarian epithelial neoplasms. Am J Obstet Gynecol 1977; 129:281-4.

14. Hughes NR. Serum concentration of G, A and M immunoglobulins in patients with carcinoma, melanoma, and sarcoma. J Nat Cancer Inst 1971; 46:1015-28.

15. Wanebo HJ. Immunology of head and neck cancer. Basic concepts. Head Neck Surg 1979; 1:42-55.

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SATELLITE SYMPOSIUM ON PEDIATRIC OTOLARYNGOLOGY

A Satellite Symposium on Pediatric Otolaryngology will be held October 17, 1983, in Tokyo. For further information, contact Keijiro Koga, Department of Otolaryngology, National Children's Hospital, 3-35-31 Taishido Satagayaku, Tokyo, Japan.

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MIDDLE EAR DISORDERS IN PATIENTS WITH ALPHA$_1$-ANTITRYPSIN DEFICIENCY

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As it is not known whether individuals with α_1-antitrypsin deficiency show increased sequelae following otitis media, 52 patients with α_1-antitrypsin deficiency were studied with respect to history of middle ear disease, presence of irreversible pathologic changes of the tympanic membranes, and hearing ability. The middle ear status was determined on otomicroscopy, tympanometry, and pure-tone audiometry. The frequency of individuals with a history of otitis media was 50%. The frequency of individuals with pathologic tympanic membrane changes was no different from that shown in the results obtained in a Swedish normal population study. Minor conductive hearing losses were found in three patients of which only one was related to a history of middle ear disease. However, the history of acute severe complications from otitis media revealed a higher frequency in those individuals with α_1-antitrypsin deficiency as compared to normals.

INTRODUCTION

Granulocyte proteolytic enzymes are, if not inactivated, capable of causing tissue destruction. In middle ear effusions of serous otitis media (OM) and acute OM, a considerable extracellular release of these enzymes has been demonstrated.[1,2] Complexes of protease inhibitors and the granulocyte proteases have been shown,[1,2] indicating active enzyme inhibition in the middle ear. In addition to a locally produced protease inhibitor, the main plasma protease inhibitors, α_1-antitrypsin (α_1-AT) and α_2-macroglobulin are present in middle ear effusions.[3] Based on quantitative immunochemical studies of middle ear effusions, α_1-AT has been suggested as the main protease inhibitor in the middle ear.[4]

Alpha$_1$-AT production is genetically determined by two codominant alleles in one gene locus, designated Pi.[5] More than 40 different Pi alleles, designated by letters of the alphabet, so far have been identified. Reduced levels of α_1-AT are associated with PiZ, PiS and some other rarely occurring alleles.[6,7] Except for the extremely rare condition of a total lack of α_1-AT, Pi$^-$ genotype, and the PiZ$^-$ genotype, the lowest serum concentrations are found in homozygote PiZ individuals, in whom serum concentrations of α_1-AT are less than 20% of normal.[8] The serum concentration of α_1-AT in homozygote PiS individuals is approximately 60% and in heterozygote PiSZ individuals approximately 40% of the normal α_1-AT concentration. The distribution of Pi phenotypes varies widely in different populations. In adult Scandinavians the frequency of the PiZ, PiS and PiSZ phenotypes is approximately 1/1,500, 1/1,500, and 1/750, respectively.[5]

Deficiency of α_1-AT is known to be associated with the destruction of alveolar tissue resulting in a high incidence of pulmonary emphysema.[9] Furthermore, α_1-AT deficiency is associated with liver diseases.[10] Conflicting data exist concerning an association with joint disease.[11,12] The aim of the present study was to elucidate whether or not individuals with α_1-AT deficiency also show an increased frequency of sequelae following otitis media (OM).

MATERIAL AND METHODS

Records of α_1-AT analyses performed between 1977 and 1981 in Södersjukhuset and in Danderyd Hospital, Stockholm, formed the basis for selection of subjects participating in this study. The indications for α_1-AT analysis had been a variety of disorders with suspected or accepted association to α_1-AT deficiency. At Södersjukhuset, α_1-AT concentrations in serum had been determined immunochemically using the Technicon Automated Immunoprecipitation Analyzer for Specific Proteins (Technicon International Division S.A.) and Commercial Protein Standard Plasma batch 1101E (Behringwerke). With this standard, the normal range of α_1-AT in serum is 1.9 to 3.5 g/L, with a mean value of 2.6 g/L (100%). All records of α_1-AT analysis with an α_1-AT concentration of less than 60% of normal serum concentration were selected, resulting in 60 available patient records. In most cases, more than one registration of deficient α_1-AT concentration in serum was available for each patient. Records of analyses of albumin, haptoglobin, and orosomucoid in serum performed simultaneously with the α_1-AT analysis, were registered for reference purposes. Forty of the 60 patients responded to a written inquiry concerning participation in a clinical investigation. Research was undertaken of health records, including ENT journals, outpatient records and hearing-aid records over the previous ten years concerning the 20 patients not replying to the inquiry. The 40 individuals participating (referred to as group A) consisted of 15 men and 25 women, with a mean age of 49 years and an age range of 18 to 81 years. The range of α_1-AT concentration in serum, expressed in percent of normal mean concentration of the technique used, was 10.4 to 57.7%, with a mean concentration of 43.5 ± 1.2 (SEM)%.

At Danderyd Hospital, serum concentrations of α_1-AT had been determined using the electroimmunoassay technique according to Laurell.[13] Commercial standard plasma (DAKO PATT AS) was used. With this standard, the normal range of α_1-AT in serum is 1.35 to 2.3 g/L with a mean value of 1.78 g/L (100%). In this hospital material, Pi-typing had been performed in most patients with low serum concentrations of α_1-AT. The Pi-typing of serum had been performed at the Malmö General Hospital, using isoelectric focusing in polyacrylamide gel.[14] All patients that were

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TABLE 1. COMPARISON OF GENERAL HEALTH STATUS IN PATIENTS WITH INTERMEDIATE TO SEVERE α_1-ANTITRYPSIN DEFICIENCY (GROUP A) AND IN PATIENTS WITH SEVERE α_1-ANTITRYPSIN DEFICIENCY (GROUP B)

Group	*General Health Status*	*No. of Patients*
A	Pulmonary disorders	8
	Joint disorders	7
	Liver disorders	4
	Allergy	4
	Malignancy	2
	Other disorders	9
	Healthy	6
	Total	40
B	Pulmonary disorders	7
	Liver disorders	1
	Pulmonary and liver disorders	2
	Joint disorders	1
	Healthy	1
	Total	12

within reach with a documented homozygote PiZ phenotype for α_1-AT deficiency, ie, 12 patients, were selected for the study and all 12 patients (six men and six women) responded to the invitation to take part in the investigation. The mean age was 46 years, range 16 to 68 years. The mean α_1-AT concentration in serum was 19.1 ± 5.6%, range 11.2 to 29.8%. This material from Danderyd Hospital is referred to as group B.

CLINICAL INVESTIGATION

The clinical investigations of both groups of patients were performed at the audiology department of Södersjukhuset. All patients were subject to a personal interview and otomicroscopy by one ENT specialist (the author). In the interview, the patients were questioned on any previous or current middle ear disease. Additional information on the general health of the patients was obtained by reviewing the available patient records. The otomicroscopic findings were categorized in four types: 1) normal tympanic membrane, 2) localized atrophy and scarring of the tympanic membrane, 3) myringosclerosis and minor retractions, and 4) myringeal adhesions and perforations. The terms *myringosclerosis* and *myringeal adhesions* refer to changes observed in the tympanic membrane.

Auditory Tests. The auditory tests were made by one skilled audiometrist in a soundproof room. Pure tone audiometry was performed using a Grason Stadler 1701 audiometer. The frequencies employed for air conduction testing were 250, 500, 1,000, 2,000, 3,000, 4,000 and 6,000 Hz. Bone conduction testing was used only in cases where air conduction thresholds equal to or greater than 20 dB were registered in the frequencies 250, 500, 1,000 and 2,000 Hz. Conductive lesion was defined as an air-bone gap of 15 dB or more for more than one frequency.

All individuals were subject to tympanometry using a Grason Stadler Otoadmittance meter 1720 with contralateral stimulation with a probe frequency of 660 Hz. Conductance (G-curve) and susceptance (B-curve) were registered. Tympanograms were automatically plotted between +400 and −400 mm H_2O on an x-y recorder. Since pathological changes of the tympanic membranes such as healed perforations are consistently recognized on the B-curve[15] the pattern of the B-curve tympanograms was used for classification in 1) normal, 2) flat, 3) negative pressure below 150 mm H_2O, 4) W-type, and 5) undulating tympanograms.[16]

Patients with bilateral pathological changes were registered according to the ear most seriously affected.

RESULTS

The 40 patients from Södersjukhuset (group A) suffered from a variety of disorders, of which pulmonary, liver, and joint diseases were the most common (Table 1). Three patients had increased serum concentrations of haptoglobin and/or orosomucoid, and four patients had a slightly reduced serum concentration of albumin. Nineteen of the patients (48%) had a history of one or more episodes of OM, 15 of them having had more than three episodes. Two patients had had mastoidectomies in the preantibiotic era, and one patient had suffered from pneumococcal meningitis of otogenic origin in 1964. A review of the health records of the individuals called but not taking part in the study revealed no documentation of middle ear disease.

The 12 patients from the Danderyd Hospital (group B) suffered mainly from pulmonary and/or liver disease (Table 1). Seven of the patients (58%) had a history of one or more episodes of OM, two of them having had three or more episodes. One patient had undergone mastoidectomy in the preantibiotic era.

No patient in either group showed any clinical signs of current middle ear infection at the time of examination. In group A, pathological tympanic membranes (type 2 to 4) were noted on otomicroscopy in five of 21 patients (24%) with no history of OM. In one of four patients (25%) with a history of one or two episodes of OM and in nine of 15 patients (60%) with a history of three or more episodes of OM, pathological tympanic membranes were noted (Table 2). Two of the latter nine patients with a history of three or more episodes of OM had been subjected to mastoidectomy. The one patient with a history of otogenic meningitis had experienced only this single episode of OM and on otomicroscopy showed normal tympanic membranes. In group B, pathological tympanic membranes were noted on otomicroscopy in two of five patients (40%) without a history of OM. In one of five patients (20%) with a history of one or two episodes of OM and one of two patients with a history of three or more episodes of OM, pathological tympanic membranes were noted (Table 3). One patient with a history of

TABLE 2. OTOMICROSCOPIC FINDINGS AND HISTORY OF OTITIS MEDIA IN GROUP A PATIENTS (N = 40)

Known Episodes of OM	*Normal Tympanic Membranes*	*Localized Atrophy & Scarring*	*Myringosclerosis & Minor Retractions*	*Myringeal Perforations & Adhesions*	*Total No. of Patients*
None	16	3	1	1	21
1 or 2 episodes of OM	3	1	0	0	4
3 or more episodes of OM	6	5	4	0	15
Total	25 (62.5%)	9 (22.5%)	5 (12.5%)	1 (2.5%)	40

TABLE 3. OTOMICROSCOPIC FINDINGS AND HISTORY OF OTITIS MEDIA IN GROUP B PiZ PHENOTYPE PATIENTS (N = 12)

Known Episodes of OM	*Normal Tympanic Membranes*	*Localized Atrophy & Scarring*	*Myringosclerosis & Minor Retractions*	*Myringeal Perforations & Adhesions*	*Total No. of Patients*
None	3	1	1	0	5
1 or 2 episodes of OM	4	1	0	0	5
3 or more episodes of OM	1	1	0	0	2
Total	8 (66.7%)	3 (25%)	1 (8.3%)	0 (0%)	12

three or more episodes of OM in group B had had a mastoidectomy but showed normal tympanic membranes.

There was general agreement between otomicroscopic findings and tympanometry (Table 4). In almost all patients with normal tympanic membranes on otomicroscopy, normal tympanograms were registered. In all patients with localized atrophy of the tympanic membranes, a W-type tympanogram was registered.

No patient in group B, but three patients in group A, showed a conductive hearing loss. The range of the mean air-bone gap in the frequencies 500, 1,000 and 2,000 Hz was 10 to 13.3 dB. One of the three patients had a history of frequent middle ear infections and had undergone a mastoidectomy The tympanic membrane showed localized atrophy on otomicroscopy and a W-type tympanogram was registered. The other two patients had no history of middle ear disease and both showed normal tympanic membranes on otomicroscopy. The tympanogram was normal in one patient and a flat tympanogram was registered in the other patient.

DISCUSSION

A protease-protease inhibitor imbalance has generally been accepted as one cause of tissue destruction. This is exemplified by alveolar tissue destruction frequently seen in patients with severe α_1-AT deficiency.[9] Individuals with intermediate α_1-AT deficiency run a greater risk of pulmonary damage in particular when additional exogenous hazardous stimuli such as cigarette smoking are present.[17] As granulocyte proteases are released in middle ear effusions, it might be suspected that individuals with α_1-AT deficiency also run a higher risk than normals of suffering destruction of middle ear structures following OM.

Alpha$_1$-AT is an acute phase reactant and serum levels rise during stimulation, ie, inflammation, pregnancy and malignancy.[18,19] Reduced levels of α_1-AT are mainly found in association with the genetic variants of α_1-AT deficiency and only rarely as a secondary feature of nongenetic etiology.[19,20] In group A, elevated concentrations of the acute phase reactants, haptoglobin and orosomucoid, found in three cases, and malignancy in two cases, indicate the possibility of increased synthesis of α_1-AT above resting levels in those individuals at the time of sampling. Thus, registered intermediate concentrations of α_1-AT (20% to 60%) can still imply a severe α_1-AT deficiency (below 20%) in a resting state. Reduced levels of α_1-AT as a secondary feature were ruled out in all individuals within this group by analyses of the general health status and laboratory findings of albumin concentrations in serum. Thus, it was concluded that group A consisted of individuals with intermediate as well as individuals with severe genetic α_1-AT deficiency. As all individuals in group B had a severe α_1-AT deficiency of the PiZ phenotype, the total material of group A and group B together can be analyzed as one material consisting of individuals with intermediate to severe genetic α_1-AT deficiency.

The frequency of OM varies widely in the literature. Better medical awareness and better availability of medical care today contribute to higher frequencies of OM in recently published prospective pediatric population studies in which the incidence of OM varies between 54% and 71%.[21-23] Furthermore, as OM is mainly a childhood disease,[24,25] the true frequency of individuals with a history of OM is difficult to obtain in retrospective analyses of adult populations such as the present study. However, it can be concluded that the individuals in this investigation, of whom 50% had a history of OM,

TABLE 4. DISTRIBUTION OF OTOMICROSCOPIC FINDINGS AND PATTERN OF TYMPANOGRAMS (B-CURVE) IN GROUP A AND GROUP B PATIENTS

	Normal Tympanic Membranes		*Localized Atrophy & Scarring*		*Myringosclerosis & Minor Retractions*		*Myringeal Perforations & Adhesions*		
Tympanograms	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*Total*
Normal	20	6	0	0	0	0	0	0	26
Flat	1	0	0	0	3	0	0	0	4
Negative pressure	0	0	0	0	0	0	0	0	0
W-shape	4	2	9	3	2	1	1	0	22
Undulating	0	0	0	0	0	0	0	0	0
Total	25	8	9	3	5	1	1	0	52
Total groups A + B	33 (63.5%)		12 (23.1%)		6 (11.5%)		1 (1.9%)		52 (100%)

do not show any lower frequency of OM as compared to normals.

The introduction of antibiotics has reduced the frequency of acute severe complications from OM. This is illustrated in a largescale population study of Swedish men born and living in Gothenburg,[26] a city with a socioeconomic and ethnical structure equivalent to that of Stockholm. The Gothenburg study consisted of statistical samples of 767 men age 60, 220 men age 50, 125 men age 30, and 260 men age 20. The frequency of individuals who in their past had undergone mastoidectomy was 1.7% in the 60-year-olds, 2.3% in the 50-year-olds, 0% in the 30-year-olds and 0.8% in the 20-year-olds. None of the individuals had been over the age of 30 years when operated upon. In the total material of 1,372 men with a mean age of 48 years, the frequency of mastoidectomies was 1.5%. In the present study, with a similar age range and mean age as the Gothenburg study, a significantly higher frequency of mastoidectomies was found, 5.8% ($p<0.05$, binomial distribution analysis). Since the incidence of OM shows no sex difference[21,24] or a higher incidence in boys than in girls,[23] the sex distribution in the present study does not contribute to this higher frequency. Including the one case with a history of otogenic meningitis in the present study, the frequency of acute severe complications from OM is still higher, 7.7%. The frequency of acute severe complications based on the number of individuals with known episodes of OM was 15.4%, which further emphasizes the higher risk found in individuals with α_1-AT deficiency. As in the present study, only living individuals suffering from disorders with accepted or suspected association with α_1-AT deficiency were studied; it is not possible to determine whether the increased risk of suffering from acute severe complications following OM in individuals with α_1-AT deficiency also implies a higher mortality risk in this disease. However, in α_1-AT deficiency population studies, no mortality from middle ear disease has been reported.[9,27]

A subsample of the Gothenburg material consisting of 767 60-year-old males was analyzed with respect to the prevalence of pathologic changes of the tympanic membranes.[28] Normal tympanic membranes were found in 63%, localized atrophy in 13%, myringosclerosis in 19%, and myringeal perforations and adhesions in 5%. Since the parameters used for classification of the pathological changes observed on otomicroscopy are identical in that and in the present study (Table 4), the results of the two studies can be compared. Chi-square analysis ($3df$) did not reveal any difference ($p>0.05$) between the two materials with respect to the distribution of the otomicroscopical findings in the tympanic membranes. Furthermore, the present study did not show any correlation between severe acute complications from OM and irreversible tympanic membrane changes. Neither did the auditory tests reveal conductive hearing losses in more than three of 52 individuals. These results thus imply that individuals with α_1-AT deficiency do not run any higher risk of developing irreversible pathologic changes of middle ear structures than do normals.

In conclusion, α_1-AT deficiency is not associated with any higher frequency of late sequelae from OM in terms of pathologic changes of the tympanic membrane or impairment of hearing. However, individuals with α_1-AT deficiency run a higher risk of suffering from acute severe complications from OM than normals do. Thus, it is recommended that patients with severe acute complications from OM should be controlled with respect to their α_1-AT phenotype.

REFERENCES

1. Carlsson B, Lundberg C, Ohlsson K. Granulocyte proteases in middle ear effusions. Ann Otol Rhinol Laryngol 1982; 91:76-81.

2. Carlsson B, Lundberg C, Ohlsson K. Granulocyte protease inhibition in acute and chronic middle ear effusions. Acta Otolaryngol (Stockh) 1983; 95:341-9.

3. Carlsson B, Lundberg C, Ohlsson K. Protease inhibitors in middle ear effusions. Ann Otol Rhinol Laryngol 1981; 90:38-41.

4. Kastenbauer E, Hochstrasser K. Experimentelle Untersuchungen zur anteiligen Hemmkapazität verschiedener Proteinasen-inhibitoren bei der Cholesteatom- und Schleimhauteiterung. Laryngol Rhinol Otol (Stuttg) 1978; 57:869-71.

5. Fagerhol M, Laurell C-B. The PiSystem-inherited variants of serum alpha$_1$-antitrypsin. Prog Med Genet 1970; 7:96-111.

6. Fagerhol M. Quantitative studies on the inherited variants of serum alpha$_1$-antitrypsin. Scand J Clin Lab Invest 1969; 23:97-103.

7. Morse J. Alpha$_1$-antitrypsin deficiency. N Engl J Med 1978; 299:1045-8.

8. Ganrot PO, Laurell C-B, Eriksson S. Obstructive lung disease and trypsin inhibitors in alpha$_1$-antitrypsin deficiency. Scand J Clin Lab Invest 1967; 19:205-8.

9. Eriksson S. Studies in alpha$_1$-antitrypsin deficiency. Acta Med Scand 1965; 177 Suppl 432:1-85.

10. Sharp HL, Bridges R, Krivit W, Freier E. Cirrhosis associated with alpha$_1$-antitrypsin deficiency: a previously unrecognized inherited disorder. J Lab Clin Med 1969; 73:934-9.

11. Cox DW, Huber O. Rheumatoid arthritis and alpha$_1$-antitrypsin. Lancet 1976; 1:1216-7.

12. Sjöblom KG, Wollheim FA. Alpha$_1$-antitrypsin phenotypes and rheumatoid diseases. Lancet 1977; 2:41-2.

13. Laurell C-B. Electroimmuno assay. Scand J Clin Lab Invest 1972; 29 Suppl 124:21-37.

14. Jeppsson J-O, Franzén B. Typing of genetic variants of α_1-antitrypsin by electrofocusing. Clin Chem 1982; 28:219-25.

15. Feldman A. Eardrum abnormality and the measurement of middle ear function. Arch Otolaryngol 1974; 99:211-7.

16. Lidén G, Harford E, Hallén O. Automatic tympanometry in clinical practice. Audiology 1974; 13:126-39.

17. Larsson C, Eriksson S, Dirksen H. Smoking and intermediate alpha$_1$-antitrypsin deficiency and lung function in middle-aged men. Br Med J 1977; 2:922-5.

18. Ganrot PO, Bjerre, B. Alpha$_1$-antitrypsin and alpha$_2$-

macroglobulin concentration in serum during pregnancy. Acta Obstet Gynecol Scand 1967; 46:126-37.

19. Jacobsson K. Studies on the trypsin and plasmin inhibitors in human blood serum. Scand J Clin Lab Invest 1955; 7 Suppl 14:55-103.

20. Mathis R, Freier E, Hunt C, et al. Alpha$_1$-antitrypsin in the respiratory-distress syndrome. N Engl J Med 1973; 288:59-64.

21. Ingvarsson L, Lundgren K, Olofsson B, Wall S. A prospective study of acute otitis media in children. 2. Incidence in an urban population. Acta Otolaryngol (Stockh) 1982; Suppl 388: 29-52.

22. Howie V, Ploussard J, Sloyer J. The "otitis-prone" condition. Am J Dis Child 1975; 129:676-8.

23. Teele D, Klein J, Rosner B. Epidemiology of otitis media in children. Ann Otol Rhinol Laryngol 1980; 89 Suppl 68:5-6.

24. Medical Research Council. Acute otitis media in general practice. Lancet 1957; 2:510-4.

25. Paavolainen M. Incidence, etiology and prognosis of acute purulent otitis media in Helsinki residents of various ages. Acta Otolaryngol (Stockh) 1967; Suppl 224:360-71.

26. Rudin R, Svärdsudd K, Tibblin G, Hallén O. Middle ear disease in samples from the general population. Acta Otolaryngol (Stockh) 1983 (in press).

27. Larsson C. Natural history and life expectancy in severe alpha$_1$-antitrypsin deficiency, PiZ. Acta Med Scand 1978; 204: 345-51.

28. Rudin R, Holmquist J. Frequency of pathologic changes in the middle ear. Ann Otol Rhinol Laryngol 1980; 89 Suppl 68: 11-3.

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ARAM GLORIG PRIZE

Dr. Aram Glorig has given audiology a lifelong inspiring, provocative, progressive, and active career in international medical, technical, and occupational audiology. A group of his friends and colleagues have established a foundation to award the Aram Glorig Prize at the biennial meetings of the International Society of Audiology. This committee, together with Dr. Glorig, will decide on candidates for the prize and its recipient. Committee members include Gunnar Liden, MD, President (Sweden); Sanford E. Gerber, PhD, Secretary-General (USA); Ole Bentzen (Denmark), and Donald Henderson (USA).

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INTERNATIONAL CONFERENCE ON HEAD AND NECK CANCER

The Society of Head and Neck Surgeons and the American Society for Head and Neck Surgery are sponsoring an International Conference on Head and Neck Cancer to be held July 22-27, 1984, in Baltimore, Maryland. The program will provide a comprehensive presentation of the present status and recent results of basic research and treatment in head and neck cancer. Abstracts are invited for oral presentations and scientific exhibits. For further information contact the Program of Continuing Education, University of Maryland School of Medicine, 10 South Pine Street, Baltimore, Maryland 21201.

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GAS ABSORPTION IN SEROUS OTITIS

A CLINICAL ASPECT

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Animal experiments have shown that gas absorption can produce a considerable intratympanic underpressure when the gas composition of the middle ear is disturbed. A similar phenomenon was observed in children with serous otitis. In 12 ears with underpressures exceeding −150 mm H_2O, Valsalva inflation or politzerization produced a transient improvement followed by a rapid return to subatmospheric pressures ranging from −130 to −300 mm H_2O. In four cases with middle ear pressures between −65 and −135 mm H_2O, the same procedure did not result in any significant underpressures. These findings suggest that inflation of the middle ear in the presence of a deep underpressure serves no purpose. It is also possible that a negative pressure, once established, can be maintained in this way.

INTRODUCTION

Despite the extremely common nature of serous otitis media, much remains to be understood about its etiology and pathogenesis. One of the cardinal questions concerns the development of subatmospheric middle ear (ME) pressures.

Recently, Cantekin et al[1] demonstrated that ME pressures in the range of −400 to −730 mm H_2O could develop in rhesus monkeys politzerized with air or oxygen gas. It was concluded from these experiments that the alteration of the gas composition in the ME cavity produced by politzerization accelerated the physiological gas absorption rate, leading to a negative intratympanic pressure. The prerequisite was that physiological ventilation of the ME via the eustachian tube (ET) be nonfunctional.

The purpose of this paper is to describe the observation of the same phenomenon in a number of school children with ME underpressures. In these children we observed that there was a gradual and relatively fast return to subatmospheric levels when normal or positive pressures had been induced by the Valsalva maneuver or politzerization. After preliminary experiments in four ears, a series of systematic observations were made 1) to establish whether the phenomenon occurred in all ears studied; 2) to ensure that the negative ME pressure developed gradually and not in a stepwise manner, as would be the case if the ME were evacuated actively; and 3) to determine the level of underpressure that could be attained.

METHODS

Sixteen ears with negative ME pressures were studied in 12 children 7 and 10 years old. Only ears in which pneumatic otoscopy had not revealed signs of effusion were included in the study. Each patient was asked to inflate his MEs by the Valsalva maneuver. Ears that could not be inflated in this manner were politzerized (ears 5, 8, and 9); in these ears a positive pressure was induced in the epipharynx with a rubber bulb while the patient was swallowing a sip of water.

In all ears the initial underpressure and the pressure attained by ME inflation were recorded. The patients, sitting in a chair in front of an examiner, were instructed to avoid yawning and sniffing during the experiment. Tympanometry was then performed at short intervals (one, two, or five minutes) until the number of recordings was sufficient to make possible a graphic representation of ME pressure as a function of time.

Most of the tympanograms were recorded with an American Electromedics tympanometer, model 85 AR, but in ears 1 and 2, an automatic digital SA-100 tympanometer (Scandinavian Audiometer AB, Malmö, Sweden) was used. The agreement between the two tympanometers had been examined previous to the study and was found to be extremely good.

RESULTS

Valsalva inflation or politzerization, as described above, changed the initial ME underpressures to pressures between +185 and −50 mm H_2O. Short interval tympanometry after inflation showed a gradual return to pathological subatmospheric levels in ears in which the initial underpressure exceeded −150 mm H_2O. After 20 minutes the ME pressures ranged from −100 to −290 mm H_2O. Our findings are shown in Figures 1, 2, and 3. For reasons of clarity recordings of three ears have been omitted, since they followed the same pattern as the others.

Inflation did not result in similar pressure levels in the four ears which had only modest initial underpressures (Fig 4). In these ears, ME pressures were between −65 and −135 mm H_2O prior to inflation, and the lowest pressure recorded 20 minutes after inflation was −85 mm H_2O.

An interesting observation (Fig 2) was made in a 7-year-old girl with ME pressures of −325 mm H_2O (ears 8 and 9). After inflation, her ME pressures

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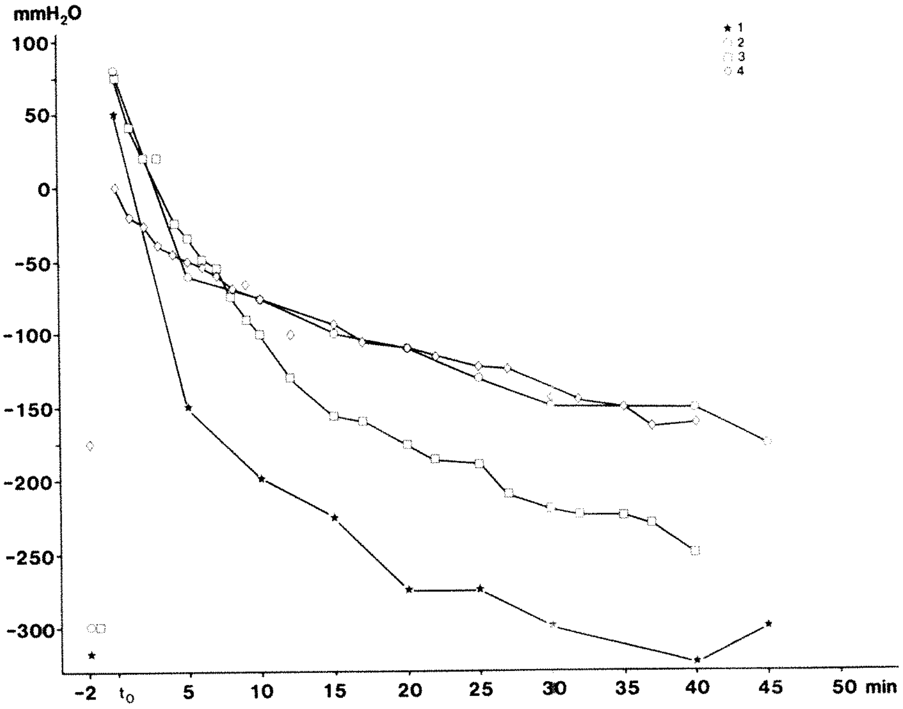

Fig 1. Recordings of middle ear pressures in ears 1 to 4 before and after Valsalva inflation. T_2 - Immediately before inflation; T_0 - Immediately after inflation.

sank to pathological levels, as was the case in the other ears with pronounced underpressures, but when levels of −190 mm H_2O had developed in both ears, she yawned intensely and equilibrated the underpressures. Following this, a new descent began. Regrettably, she would not permit further tympanometry, but the recordings obtained suggest that negative ME pressures would develop even after equilibration.

DISCUSSION

The ME cavity can be considered an "open nonventilated" or "intermittently ventilated gas pocket" in which oxygen and nitrogen are constantly absorbed.[2] In principle, gas exchange may occur in four ways: 1) diffusion across the capillaries of the mucosa; 2) diffusion across the tympanic membrane; 3) passage via the ET; and 4) diffusion through the round window.

Studies by Elner[3] indicate, however, that gas diffusion through the normal tympanic membrane is negligible. Experiments using widely different methods[2] seem to agree that about 1 ml of gas is absorbed from the ME per 24 hours. The minute underpressure, continuously generated by gas absorption, is equilibrated by the intermittent openings of the ET. Air volumes entering the ME in this way suffice to equilibrate the underpressure, but are too small to affect the gas consumption within it.[2]

Consensus probably exists concerning the interaction between gas absorption, generation of a minute underpressure, and equilibration of the underpressure in a normal ME possessing a well-functioning ET. In serous otitis, on the other hand, the possible role of gas absorption is a matter of much controversy. According to the traditional concept, dysfunction of the ET, ie, either mechanical or functional obstruction, prevents the physiological ventilation of the ME. Under these circumstances, the underpressure generated by the continuous gas absorption is not equilibrated, but grows to pathological levels. It is thought that a pathological underpressure can cause effusion per se,[4] and that it may have a harmful effect on the ME mucosa. No conclusive evidence in support of this theory has been presented to date. The fundamental problem is to definitely determine the composition of the gas and the rate of gas exchange in the ME cavity under normal and abnormal conditions.

Some data supporting the theory do exist, however. Cantekin et al[5] demonstrated in rhesus monkeys that functional obstruction of the ET produced by transection or expunction of the tensor veli palatini muscle caused significant ME underpressures. Tos and Bonding[6] have shown that nasotracheal or nasogastric intubation in humans produces a considerable ME underpressure that remains for some time after extubation. They ascribed their findings to mechanical obstruction of the ET orifice and to internal tubal occlusion caused by irritation of the mucosa. The fact that patients with malignancies in the epipharynx frequently have ME effusions on the affected side may be explained by similar mechanisms. It has been demonstrated that posterior nasal packing in patients with epistaxis also results in pathological ME pressures.[7,8]

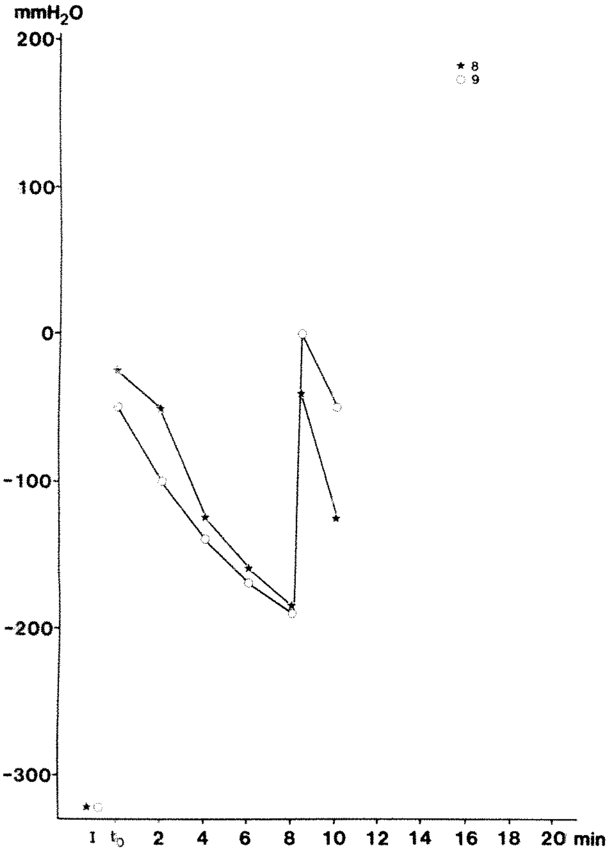

Fig 2. Recordings of middle ear pressures in ears 8 and 9. I - Immediately before politzerization; t$_0$ - Immediately after politzerization. Patient yawned after eight minutes, which opened eustachian tubes and equilibrated ME pressure.

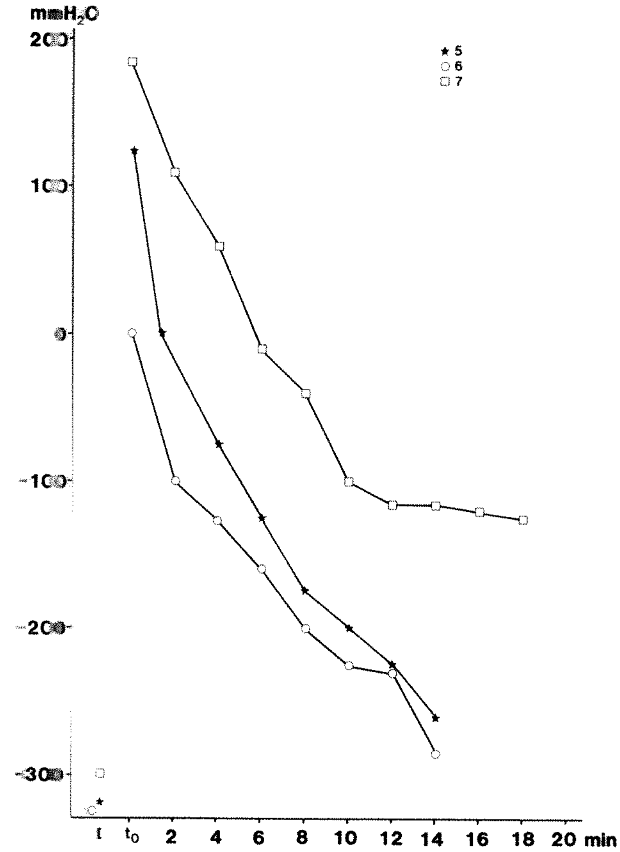

Fig 3. Recordings of middle ear pressures in ears 5 to 7 before and after either Valsalva maneuver or politzerization. I - Immediately before; t$_0$ - Immediately after.

The pathogenic role of gas absorption in serous otitis media has been questioned by Buckingham and Ferrer,[9] who, by using direct measuring methods, reported ME pressures ten times smaller than those recorded by tympanometry in ears with serous otitis. There is also opposition to this theory from Magnuson,[10] who denies that gas absorption can produce the deep underpressures seen in serous otitis and who has proposed a new theory stating that negative ME pressures are generated by active evacuation of the ME by sniffing.

Our study showed that inflation of MEs with underpressures exceeding -150 mm H_2O resulted in normal or positive pressures rapidly followed by a return to pathological levels. Although escape of gas through the ET may have contributed to reduction of the positive pressures, it seems safe to assume that negative pressures were caused by gas absorption in the ME, since active evacuation by means of sniffing can be ruled out for the following reasons. All individuals studied were under continuous observation to ensure specifically that sniffing did not occur. All curves followed the same general pattern, indicating a gradually decreasing ME pressure. The recordings in Figure 1, where one-minute intervals were used, preclude the possibility of a stepwise pressure change. Even where longer intervals were used, most of the decrements are smaller than those seen in sniffing.

The shapes of the curves representing ME pressure in this study resemble those in Cantekin et al's animal experiments.[1] Pathological values were, however, reached much faster in our study. This can be explained by the fact that the children had underpressures in their ears at the beginning of the experiment, which was not the case in Cantekin et al's monkeys. The presence of a considerable negative pressure in a ME implies that the amount of gas in the ear is small. Consequently, the gas composition is deranged more by a Valsalva maneuver than is the gas of a normally aerated ME, providing that the same volume is inflated. Cantekin et al,[1] found that the rate of gas absorption depended on the degree to which the original gas composition was disturbed. Accordingly, a faster pressure reduction was expected in the children we studied.

The ears depicted in Figure 4 had only modest or slight underpressures, ie, -65 to -135 mm H_2O. In these ears no significant negative pressures were recorded. The observation period may, however, have been too short to allow a definite conclusion about the final pressure level. Apparently, the gas compositions were not disturbed enough to elicit fast absorption.

Since the Valsalva maneuver and politzerization only produced pathological underpressures in ears which already had considerable underpressures, the presence of the original underpressures has still to be explained.

Cantekin et al,[1] proposed a theory in which derangement of the gas composition in the ME cavity plays a central role. They hypothesized that the intervals between the openings of the ET may be prolonged in conditions of tubal dysfunction. Due to continuous gas absorption in the ME, the pressure gradient between the ME and the epipharynx will increase and cause larger than normal volumes of air to enter the ME at each opening of the tube. This may derange the gas composition in the cavity, accelerate gas absorption, and lower the intratympanic pressure. The new underpressure will set up a new gradient, initiating a vicious circle which leads to a pathological ME pressure.

A different view is taken by Magnuson,[10] who has established that active evacuation by means of sniffing can produce considerable intratympanic underpressures. The two theories are not necesarily exclusive and may even be combined to a certain extent. In a common cold, for instance, the ME is often evacuated when a sniff is performed, probably due to pressure gradients following nasal obstruction. If equilibration of such an underpressure because of tubal dysfunction necessitates a Valsalva inflation, a process of gas absorption, as demonstrated in this study, may be started. It is also conceivable that nasal obstruction in a common cold may elicit a Toynbee phenomenon upon swallowing and may thus induce a negative ME pressure. Tubal dysfunction may then have the same consequences as suggested above.

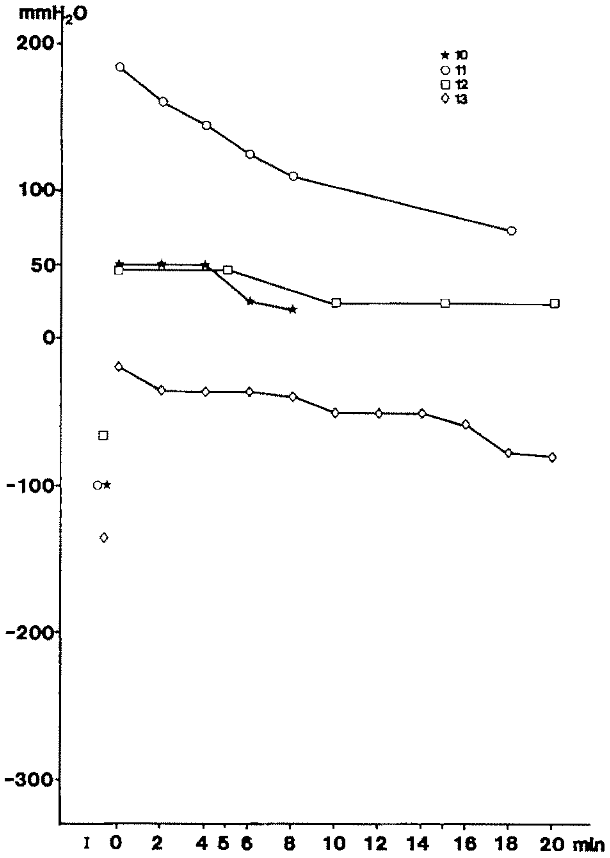

Fig 4. Recordings of middle ear pressures in ears 10 to 13 before and after Valsalva inflation. I - Immediately before; 0 - Immediately after.

CONCLUSION

Our findings suggest that Valsalva inflation or politzerization in ears with deep underpressures may initiate a process of gas absorption leading to a fast restoration of the underpressure. Accordingly, inflation of the ME may not be beneficial in the treatment of serous otitis. It is also implied that inflation of the ME should not be employed in experiments testing the ability of the ET to equilibrate a positive intratympanic pressure. Finally, it can be assumed that gas absorption induced in this way may play an important role in maintaining an already existing ME underpressure.

REFERENCES

1. Cantekin EJ, Doyle WJ, Phillips DC, Bluestone CD. Gas absorption in the middle ear. Ann Otol Rhinol Laryngol 1980; 89 Suppl 68:71-5.

2. Elner Å. Quantitative studies of gas absorption from the normal middle ear. Acta Otolaryngol (Stockh) 1977: 83:25-8.

3. Elner Å. Gas diffusion through the tympanic membrane. Acta Otolaryngol (Stockh) 1970; 69:185-91.

4. Flisberg K. The effects of vacuum on the tympanic cavity. Otolaryngol Clin North Am 1970; 3:3.

5. Cantekin EJ, Bluestone CD, Saez CA, Doyle WJ, Phillips DC. Normal and abnormal middle ear ventilation. Ann Otol Rhinol Laryngol 1977; 86 Suppl 41:1-15.

6. Tos M, Bonding P. Middle ear pressure during and after prolonged nasotracheal and/or nasogastric intubation. Acta Otolaryngol (Stockh) 1977; 83:353-9.

7. McCurdy MJA. Effects of nasal packing on eustachian tube function. Arch Otolaryngol 1977; 103:521-3.

8. Tos M, Bonding P. Middle ear pressure during brief pathological conditions of the nose and throat. Acta Otolaryngol (Stockh) 1981; 92:63-9.

9. Buckingham RA, Ferrer JL. Observations of middle ear pressures. Commentary with movie. Ann Otol Rhinol Laryngol 1980; 89 Suppl 68:56-61.

10. Magnuson B. On the origin of the high negative pressure in the middle ear space. Am J Otolaryngol 1981; 2:1-12.

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X-RAY STUDY OF THE MONTH

METASTATIC CARCINOMA OF THE THYROID TO THE SPHENOID SINUS

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PATIENT

The patient is a 50-year-old woman with a history of papillary and follicular carcinoma involving the right lobe of the thyroid, adjacent soft tissues and lymph nodes. In 1974 she underwent total thyroidectomy and right radical neck dissection. On this admission she presented with intermittent epistaxis, weight loss of 4.5 kg over a period of 6 months and pain in the right nasopharyngeal region. Physical examination revealed a mucosa-covered mass filling the nasopharynx.

RADIOGRAPHIC FINDINGS

On admission a chest x-ray study showed a diffuse, bilateral nodular pattern consistent with metastasis from thyroid carcinoma (Figure, A). Plain films and polytomes of the nasal cavity and nasopharynx in both the AP and lateral projections revealed a soft tissue mass in the sphenoid sinus (Figure, B, lateral polytome, arrows) eroding the basisphenoid and extending into the nasopharynx (Figure, B, arrowheads). There was also erosion of the sellar floor (Figure, C, lateral polytome, arrowheads). A computerized tomography (CT) scan with contrast enhancement in the axial plane (Figure, D) revealed a soft tissue mass in the sphenoid sinus extending into the posterior ethmoid sinuses (small arrowheads) and the sella (large arrowheads).

DIAGNOSIS

The findings of both the polytomes and CT scan at this admission were thought to represent a mucocele or primary tumor of the sphenoid sinus with extension into the nasopharynx, ethmoid sinuses and sella. At surgery, a left lateral rhinotomy, septectomy, left ethmoidectomy and left sphenoidectomy were performed. The pathological diagnosis was follicular carcinoma with papillary foci consistent with metastasis from the resected primary thyroid carcinoma.

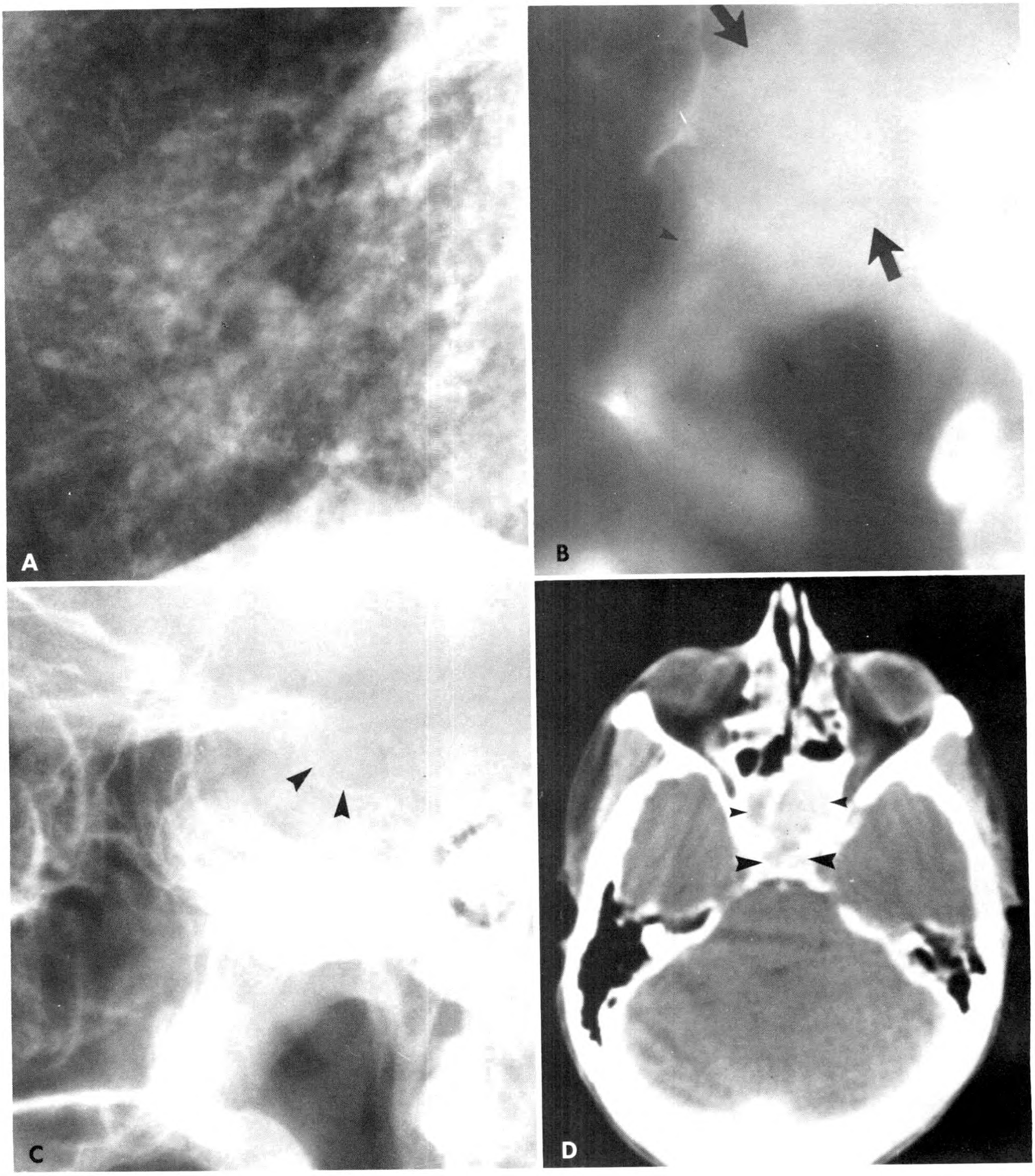
DISCUSSION

Papillary carcinoma of the thyroid is slow-growing and metastasizes via lymphatics to regional lymph nodes and rarely to distant sites. Follicular carcinoma of the thyroid grows slowly and metastasizes via vascular channels, especially to bone and lung.[1,2] Metastatic carcinoma to the sinonasal tract is extremely rare. The most complete review of this subject was done by Bernstein et al in 1966 in which they reported only 82 cases in the world literature, including ten of their own. Of these 82 cases, only 3.8% had thyroid primaries.[3] Metastatic tumors to the paranasal sinuses arise most commonly from adenocarcinoma of the renal parenchyma (hypernephroma). Other sites of origin are breast, lung, testes and thyroid in that order. Sites of upper airway tract involvement in decreasing order of frequency are the maxillary, ethmoid, frontal sinuses, and the nasal cavity. The sphenoid sinus, nasopharynx, hard palate and alveolar ridge are much less common locations.[3,4]

Lesions in the sphenoid sinus, remaining paranasal sinuses, nasal cavity and nasopharynx may represent metastatic disease. Frequently, no clinically distinctive features are present; metastatic disease may present with local pain and epistaxis, as in the case of our patient.[5,6] Unfortunately, there are no specific radiographic findings to differentiate metastatic from primary sinus lesions. Metastatic and primary tumors can invade soft tissue and destroy bone. Plain films and polytomes can delineate the extent of bone destruction. The axial contrast-enhanced CT scan can further delineate the intracranial and orbital extension of the tumor. A careful history of previous malignancy is therefore helpful in making the correct diagnosis. Other lesions that may present in this region are mucocele, chordoma, primary sphenoid sinus carcinoma, nasopharyngeal carcinoma, plasmacytoma, adenoidcystic carcinoma, pituitary adenoma and giant cell granuloma.

From the Departments of Radiology (Chang, Weber) and Otolaryngology (Pappanikou), Harvard Medical School, Boston.

REPRINTS — Gloria Chang, MD, Department of Radiology, Harvard Medical School, Boston, MA 02114.



REFERENCES

1. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Classification and prognosis of thyroid carcinoma. Am J Surg 1961; 102:354-87.

2. Frazell EL, Foote FW Jr. Papillary cancer of the thyroid. Cancer 1958; 11:895-922.

3. Bernstein JM, Montgomery WW, Balogh EK Jr. Metastatic tumors to the maxilla, nose and paranasal sinuses. Laryngoscope 1966; 76:621-50.

4. Nahum AM, Bailey BJ. Malignant tumors metastatic to the paranasal sinuses: case report and review of the literature. Laryngoscope 1963; 73:942-53.

5. Cinberg JZ, Terrife D. Follicular adenocarcinoma of the thyroid in the maxillary sinus. Otolaryngol Head Neck Surg 1980; 88:157-8.

6. Cinberg JZ, Solomon MP, Ozbardacki G. Thyroid carcinoma and secondary malignancy of the sinonasal tract. Arch Otolaryngol 1980; 106:239-41.

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PATHOLOGY CONSULTATION

PLASMA CELL TUMORS OF THE HEAD AND NECK

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In order of frequency, the plasma cell lesions affecting the head and neck are multiple myeloma, extramedullary plasmacytoma, plasma cell granuloma, and solitary plasmacytoma of bone. All except plasma cell granuloma are neoplastic and they are interrelated. The solitary plasmacytoma of bone is regarded as a form of multiple myeloma. The extramedullary plasmacytoma may be a lesion of local significance only or may terminate in a disseminated disease, myelomatosis, that differs clinically and prognostically from multiple myeloma.

A localized plasma cell lesion in the head and neck poses considerable diagnostic and therapeutic problems for the head and neck surgeon. While there is a rather abundant literature on these tumors, the authors have either perpetuated the opinions of others or have indiscriminately lumped the several categories of disease into one.

Confronted with a plasma cell tumor, the head and neck surgeon has several, yet a limited number of, diagnostic options: 1) a localized manifestation (bone or soft-tissue) of existing systemic disease, *multiple myeloma*; 2) an *extramedullary plasmacytoma* without evidence of systemic disease; 3) a localized, intraosseous lesion, *solitary plasmacytoma of bone;* or 4) a benign inflammatory lesion having no relationship to the preceding three disorders, the *plasma cell granuloma*. Each of these lesions will be discussed, but the integral cell, the plasma cell, requires definition.

Plasma cells are now widely accepted as the secretory form of B-lymphocytes, differing principally by the presence of abundant protein-synthesizing equipment in the cytoplasm. Plasma cell diseases are a group of clinical disorders characterized by growth of a single clone of cells that elaborates a single, homogeneous immunoglobulin molecule. The most important and numerous of these diseases is multiple myeloma. It may be regarded as a malignant plasma cell disorder arising from a single transformed cell of the B-cell series of lymphocytes.

Neoplastic proliferation of this single line of plasma cells produces a specific protein, as if under constant antigenic stimulation. Because a specific globulin is produced that is unique for each patient, the plasma cell diseases are also referred to as monoclonal gammopathies. The monclonal protein is comprised of one heavy-chain class (IgG, IgA, IgM, IgD, or IgE) and one light-chain class (κ or λ), and is often referred to as an M (myeloma protein).

Diagnosis of plasma cell dyscrasias is based on the combination of clinical, radiologic and clinical laboratory evaluations. In the latter, the presence and classification of the paraproteinemia is most important and definitive. Production and detection of the paraproteinemia is, however, not uniform. Nonsecretory forms exist and detection is clearly based on tumor mass or tumor burden, a factor very important in localized plasmacytomas.

PLASMA CELL GRANULOMA

Plasma cell granuloma is the least controversial of the plasma cell tumors. It has a predilection for the oral cavity. Because of the numbers of plasma cells normally present in the upper aerodigestive tracts, their presence in reactive and inflammatory lesions is expected. In instances where they are unusually abundant in such reactions, the designation *plasma cell granuloma* is applied as a diagnostic term. In the oral cavity, plasma cell granuloma is a lesion primarily of the periodontal tissues. The gingiva is the area most frequently involved, with maxillary and mandibular gingivae equally affected. The tumors are seen on the marginal, interdental and attached gingiva; alveolar mucosa is spared.

Bone loss may or may not be present. There is no sex predilection and the lesions can occur at any age. Multiple plasma cell granulomas are rare. Recurrences are dependent on the underlying cause of the reactive lesions.

Microscopically, plasma cell granulomas can be distinguished from plasmacytoma. The stromal matrix is vascular and reactive. The plasma cells, while numerous, do not exist in pure or nearly pure "culture" and are accompanied by other inflammatory cells. The plasma cells show no cytologic abnormalities and are usually concentrated in areas surrounded by connective tissue septae. Russell bodies may be present.

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REPRINTS — John G. Batsakis, MD, Chairman, Department of Pathology, M. D. Anderson Hospital, Texas Medical Center, Houston, TX 77030.

SOLITARY PLASMACYTOMA OF BONE

Solitary plasmacytoma of bone is now recognized as a rather unusual presentation of multiple myeloma.[1,2] For this reason and because its presentation in facial bones is uncommon, it is the second least controversial of the plasma cell disorders. Patients with solitary plasmacytoma of bone are defined as having a radiographically solitary lytic lesion and no evidence of plasmacytosis in a random bone marrow examination. Detection of a paraprotein or M-band in serum or urine does not exclude the diagnosis.[1,2] There is no absolute proof that any such lesion is indeed "solitary." The spine, pelvis, and femur are the sites of predilection. There is a male preponderance and the average age of onset is about one decade less than that for multiple myeloma.[1,2]

The radiographic appearance is usually a multicystic area of rarefaction. Compared with the sharply demarcated, destructive lesions of multiple myeloma, the solitary plasmacytoma is characterized as being larger, trabeculated, and multilocular.

The presence of protein abnormalities is obviously important for follow-up. If a paraprotein is present, it should disappear after primary treatment. Persistence or reappearance indicates residual tumor or dissemination.

Dissemination is nearly always an event that occurs in the first 3 to 5 years after primary diagnosis.[2] Nearly 50% of the patients exhibit this spread of disease which is almost exclusively skeletal.[1,2] Extramedullary spread is quite unusual. After dissemination, the clinical, pathologic and laboratory findings are indistinguishable from multiple myeloma. Although a definite percentage of patients with solitary plasmacytoma of bone manifest no recurrences after treatment and have no dissemination of their disease, they should be considered as always at risk for multiple myeloma.[1,2]

MULTIPLE MYELOMA

In contrast to the low incidence of solitary plasmacytoma of bone in the jaw bones, radiographic evidence of such involvement by multiple myeloma is not uncommon and is estimated at nearly 30%.[3] The jaw lesions appear as multiple, noncorticated, small, osteolytic lesions. They vary in size from 1 to 3 mm and seldom exceed 1 cm. Confluence of the lesions is rarely seen. In up to 15% of cases of multiple myeloma, the jaw lesions may be the primary manifestation of the disease.[3] Both maxilla and mandible may be affected, but the mandible is most often the site. In the mandible, the initial lesions tend to appear in the posterior region where marrow spaces are largest and extend forward and below the mandibular canal. There is also extension up into the marrow spaces of edentulous regions and into the ramus.

EXTRAMEDULLARY PLASMACYTOMA

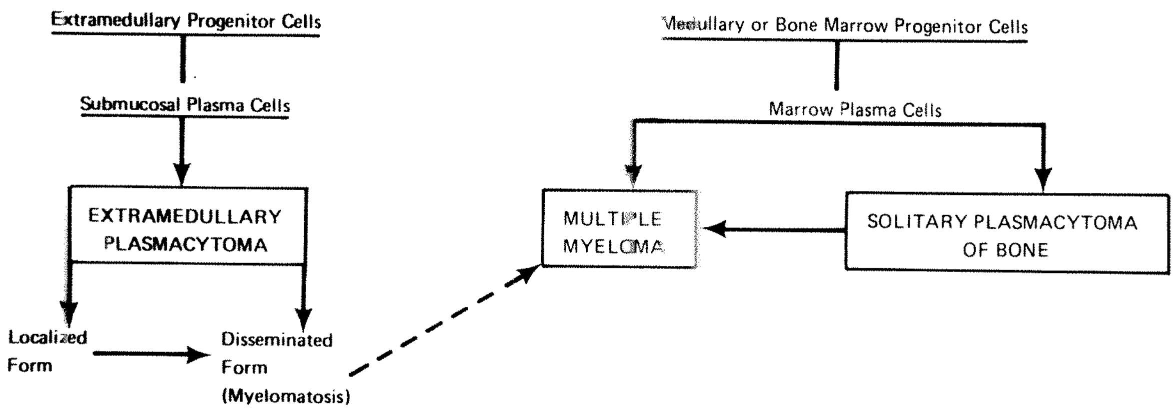
Extramedullary plasmacytoma is the term applied to plasma cell tumors which present outside of bone.[1,2,4] Tumors arising in the skeleton which have broken out through the cortex to form an associated soft tissue mass are excluded. Of all extramedullary plasmacytomas, up to 80% have been recorded as arising in the upper air passages and oral cavity.[4] They represent nearly 4% of all nonepithelial neoplasms of the nasal cavity, nasopharynx, and paranasal sinuses.[5] Arising in submucosal tissues in these sites, the plasmacytoma presents as a fleshy, yellow-gray to dark red, sessile, polypoid or pedunculated tumor. Ulceration is not frequent but underlying bone may be involved.

Between 10% to 20% of upper aerodigestive tract plasmacytomas will manifest multiple lesions in the head and neck, eg, nasopharynx and nasal cavity or larynx and pharynx.[1]

The biologic behavior of an extramedullary plasmacytoma of the upper aerodigestive tract can fall into one of several patterns: 1) localized solitary disease, controlled by surgery, radiotherapy, or both, and which does not recur or become disseminated; 2) locally recurrent disease, controlled by additional therapy; 3) aggressive, persistent, or recurrent disease producing death of the host through uncontrollable local extensions; 4) local disease with "metastatic" involvement of regional lymph nodes but without evidence of distant spread; and 5) local disease, recurrent or otherwise, followed by dissemination and development of multiple plasma cell neoplasms and/or multiple myeloma. Assessed by clinical stage, localized and controllable plasmacytomas are stage I. Stage II disease includes those tumors with local extension and/or involvement of lymph nodes. Disseminated disease is stage III. With an increase in stage, the probability of serum and urine abnormalities being detected increases. This relates to tumor mass and not to the cellular composition, since each plasmacytoma elaborates its own monoclonal proteins.[6,7]

Histologic appearance cannot be used as a reliable indicator of biologic activity.[4] The typical extramedullary plasmacytoma consists of a monocellular proliferation of plasma cells set in a very sparse matrix. Cellular and nuclear atypia may be minimal or prominent. Binucleate and trinucleate cell forms may be present and in some fields only a proximity to more definable plasma cells allows definition of the cells. Local amyloid is found in about 15% of the cases, but systemic amyloidosis is very unusual.

In the most comprehensive review to date, Wiltshaw[1] indicates that 40% of extramedullary plasmacytomas spread beyond the presenting site and its drainage lymph nodes. Of these, 81% developed lesions in bone (most often single and randomly distributed) and 62% had soft tissue and visceral de-


Extramedullary Progenitor Cells
Submucosal Plasma Cells
EXTRAMEDULLARY PLASMACYTOMA
Localized Form
Disseminated Form (Myelomatosis)
Medullary or Bone Marrow Progenitor Cells
Marrow Plasma Cells
MULTIPLE MYELOMA
SOLITARY PLASMACYTOMA OF BONE

Proposed interrelationships of plasma cell tumors of head and neck.

posits. The spread to bone demonstrates no preference for active hematopoietic tissue, such as myeloma prefers, and is rarely as widespread or diffuse as that seen in patients with multiple myeloma.

The variable patterns of behavior of extramedullary plasmacytomas set them apart from the other plasma cell disorders, but the reasons for this are hard to find.[1-7] The low tumor burden is certainly accountable for the normal or near-normal immunoglobulins and the usual absence of detectable myeloma proteins. The predominance of IgG-containing plasma cells in the nasopharynx and upper airway may also be an ameliorating factor since myeloma patients with IgG have better therapeutic responses and survival than do patients with an IgA myeloma.[6] The reported good response to chemotherapy in patients with disseminated disease from extramedullary plasmacytomas differs from the poor survival manifested by most patients with multiple myeloma.[1] There is an overall survival rate of more than 50% at ten years for extramedullary plasmacytoma patients.[1] Finally, plasma cell dyscrasias originating from extramedullary sources tend to behave more like lymphoreticular neoplasms than multiple myeloma. The regional lymph node involvement and nodular rather than diffuse bone marrow involvement speak to that hypothesis.[1-8]

The Figure summarizes the interrelationships of the plasma cell tumors affecting the head and neck. The Figure acknowledges the possibility of evolution of extramedullary plasmacytoma to multiple myeloma but relates the differences in the dissemination pattern and better prognosis to the disorder *myelomatosis* as distinct from multiple myeloma.

SUMMARY

Neoplastic plasma cell disorders, multiple myeloma, extramedullary plasmacytoma and solitary plasmacytoma affect the head and neck with different manifestations. Multiple lytic lesions of the jaws and infrequent soft-tissue lesions characterize multiple myeloma's presence. The solitary plasmacytoma of bone is infrequent in the jaws. Wherever it occurs, it is a precursor lesion to multiple myeloma. Extramedullary plasmacytoma has several clinical and biologic forms. The most benign is the local upper airway lesion that is amenable to surgery or radiotherapy and manifests no recurrences. Approximately 40%, however, terminate in osseous and soft-tissue dissemination. The distant involvement has more characteristics of metastases than the diffuse axial skeletal involvement of multiple myeloma; to acknowledge this distribution and the apparently better prognosis, the disseminated form is called myelomatosis.

REFERENCES

1. Wiltshaw E. The natural history of extramedullary plasmacytoma and its relation to solitary myeloma of bone and myelomatosis. Medicine (Baltimore) 1976; 55:217-38.

2. Woodruff RK, Malpas JS, White FE. Solitary plasmacytoma: II. Solitary plasmacytoma of bone. Cancer 1979; 43: 2344-7.

3. Bruce KW, Royer RQ. Multiple myeloma occurring in the jaws: a study of seventeen cases. Oral Surg 1953; 6:729-44.

4. Batsakis JG, Fries GT, Goldman RT, Karlsberg RC. Upper respiratory tract plasmacytoma: extramedullary myeloma. Arch Otolaryngol 1964; 79:613-8.

5. Fu Y-S, Perzin KH. Nonepithelial tumors of the nasal cavity, paranasal sinuses & nasopharynx: a clinicopathologic study: IX. Plasmacytomas. Cancer 1978; 42:2399-406.

6. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma: correlation of measured myeloma cell mass & presenting clinical features, response to treatment, and survival. Cancer 1975; 36:842-54.

7. Woodruff RK, Whittle JM, Malpas JS. Solitary plasmacytoma: I. Extramedullary soft tissue plasmacytoma. Cancer 1979; 43:2340-3.

8. Marsch WC, Gross UM. Frequency and pathomorphology of extramedullary manifestations in plasma cell myeloma of the skeleton. Path Res Practice 1978; 163:115-27.

ABSTRACTS FROM THE *ANNALS OF INTERNAL MEDICINE*[*]

Preventing Severe Heat Injury in Runners: Suggestions From the 1979 Peachtree Road Race Experience

By *A. C. England, D. W. Fraser* and *A. W. Hightower.* Ann Intern Med 1982; 97:196-201.

Of an estimated 17,632 participants of the 1979 Peachtree Road Race, a 10-km race held at 0800 on 4 July in Atlanta, Georgia, 29 had severe heat injury (collapse with altered mental status and rectal temperature of 39.7°C or greater); all 29 recovered promptly. The temperature was 24.0°C; the relative humidity, 83%; and the wet bulb-globe index, 23.0°C. Compared with unaffected participants matched by age, sex, and predicted finishing time, case-runners were taller, had slower best recent 1.6-km and 10-km times, had run less in June, were more likely to achieve 89% of estimated maximum aerobic capacity during the race, less often splashed with water, were more likely to have underestimated their predicted finishing times based on their best recent 10-km times, and were more likely to live in Georgia. Height, sprinkler use, and underestimating predicted finishing times were each significant in the presence of the others. These observations suggest that participants of similar races, particularly those taller than 179.2 cm, should splash with water at least twice and base their predicted finishing times on their best recent 10-km times; adherence to these recommendations by runners at risk should reduce their severe heat injury risk at least 8.1 times.

Scintigraphic Thyroid Abnormalities after Irradiation: A Controlled Study with ^{99m}Tc Pertechnetate Scanning

By *C. Gonzalez-Villalpando, L. A. Frohman* and *C. Bekerman*, et al. Ann Intern Med 1982; 97: 55-8.

We did ^{99m}Tc-pertechnetate thyroid scintigraphy on 99 subjects with no history of therapeutic irradiation to the head or neck. They were compared with 198 irradiated patients selected from a group of over 1,700 who were evaluated because of radiation treatment for benign head and neck conditions during childhood. The two groups were similar with respect to age and sex distribution. There were significantly more abnormal scintigrams in the irradiated group (55 of 198 patients versus one of 99 controls). Even after patients and controls with palpable nodules were excluded from the analysis there were still more abnormal scintigrams in the irradiated group (16 of 150 irradiated versus one of 97 control subjects). We conclude that thyroid nodules, including the smaller, nonpalpable nodules discovered by scintigraphy, are related to previous radiation therapy. For persons at substantial risk, such as those who received high-dose treatment (greater than 700 R) during childhood, the data support the use of screening scintigraphy, even with normal findings on palpation.

Treatment of Infections due to Methicillin-resistant *Staphylococcus Aureus*

By *C. Watanakunakorn.* Ann Intern Med 1982; 97:376-8.

Strains of methicillin-resistant *Staphylococcus aureus* are resistant to other penicillins. The in-vitro susceptibility to the cephalosporins differs among strains. Some strains, susceptible to cephalosporins by the standard disk susceptibility test, are proved resistant by the quantitative dilution test; they may show pop-up colonies within the zone of inhibition when incubated further at room temperature. The clinical efficacy of the cephalosporins with or without an aminoglycoside in treating infections due to methicillin-resistant S. *aureus* is in doubt. To date, all strains of methicillin-resistant S. *aureus* have been susceptible to vancomycin. In-vitro antagonism of vancomycin and rifampin against S. *aureus* has been shown. Thus, vancomycin alone appears to be the treatment of choice; if this treatment fails, aminoglycoside or rifampin should be added. Serum bactericidal titers should be carefully monitored before and after the addition of the new agent and in-vitro time-kill studies of combination of antibiotics done if feasible.

Herpes Simplex Virus Pneumonia: Clinical, Virologic, and Pathologic Features in 20 Patients

By *P. G. Ramsey, K. H. Fife, R. C. Hackman, J. D. Meyers* and *L. Corey.* Ann Intern Med 1982; 97:813-20.

Herpes simplex virus (herpesvirus) was isolated from autopsy lung specimens of 20 patients with clinical, roentgenographic, and histologic evidence of pneumonia. Mucocutaneous herpesvirus infection preceded the onset of pneumonia in 17. Twelve patients had focal pneumonia, 10 of whom had concomitant herpetic tracheitis, esophagitis, or both. Eight patients had diffuse interstitial pneumonia, six of whom had dissemination of herpesvirus to other organs. Of the eight lung isolates available for typing, seven were herpesvirus-1 and one, herpesvirus-2. A high prevalence of herpesvirus antibody in serum samples obtained before pneumonia and identical restriction endonuclease patterns between mucosal and lung isolates in individual patients indicated that, in most cases, herpesvirus pneumonia was due to endogenous reactivation of virus. Focal herpesvirus pneumonia appeared to result from contiguous spread of herpesvirus to lung parenchyma, whereas diffuse interstitial pneumonia appeared to be a manifestation of hematogenous dissemination of virus.

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[*] *Selected from articles of general interest in a regular exchange.*

JOSEPH H. OGURA
1915-1983

Joseph H. Ogura, MD, died on April 14, 1983. He was 67 years old and is survived by his wife Ruth, daughter Susan Bell, and sons Peter and John.

Dr Ogura contributed greatly to the field of otolaryngology. He was a masterful and talented surgeon and excelled in basic and clinical research. As a young surgeon he was not satisfied with the current surgical techniques of the day and he questioned many accepted principles of therapy. Because of this questioning intellect, he became a pioneer in conservation surgery of the larynx. His surgical approach was based upon extensive and thorough study of laryngeal anatomy and pathology. He devised and popularized various surgical approaches for preserving laryngeal function in select cases of cancer of the larynx and pharynx. He originally encountered criticism from his colleagues, but his persistence and careful documentation of the preoperative evaluation, operative technique, and survival eventually resulted in worldwide acceptance. Therefore hundreds of patients had partial laryngectomies with preservation of function rather than total laryngectomies, without sacrificing the chance of survival. Dr Ogura's interest in airway physiology, endocrine exophthalmus, laryngeal trauma, and reconstructive techniques of head and neck surgery also resulted in improved methods of treatment for his patients.

Dr Ogura's most important contribution to medicine was as an educator. He established a rigid training program for residents and postgraduate students. His primary objective was to train and sponsor outstanding otolaryngologists who would pursue a career in academic otolaryngology. He was able to attain this goal because he was a tireless worker, innovative thinker, and superior teacher who also had that rare ability to stimulate his students to achieve their maximum potential. Dr Ogura's greatest legacy to medicine will not necessarily be the hundreds of scientific publications, invited lectures, awards, or prominent positions held, but rather the large number of his students who have become educators.

Hugh F. Biller, MD
Max Som, MD

BOOK REVIEWS

Neuronal Mechanisms in Hearing

Edited by *Josef Syka* and *Lindsey Aitkin*. Hard cover, black and white illustrations, indexed, 443 pages, 1981. Plenum Press, New York. Price $45.00.

This volume presents the papers from a symposium on auditory neurophysiology held in Prague in July 1980. Although there is a strong emphasis on electrophysiology, there are also a few behavioral and neuroanatomical papers; several of the latter present results obtained with the 2-deoxyglucose technique. The book contains a variety of material, but some important areas such as direct measurement of basilar membrane motion, are underrepresented. While there are some excellent chapters, the overall quality of the contributions is uneven. A brief overview of the seven major topic headings follows.

A diverse group of papers is included under the heading "Cochlear Mechanisms." In one of the better of these, Russell and Sellick present their recent findings on velocity and displacement responses in cochlear hair cells.

In the section called "Coding in the Auditory Nerve and Cochlear Nucleus," several papers stand out. The neural circuitry of the dorsal cochlear nucleus is discussed by Osen and Mugnaini, and by Young and Voight. Problems related to the restricted dynamic range of primary auditory fibers and to the coding of complex sounds were considered by other contributors, including Voight, Sachs, Young, and Evans.

The papers on "Central Auditory Mechanisms" are dominated by several informative studies of the inferior colliculus and the medial geniculate body. Aitken et al report the results of combined electrophysiological — neuroanatomical studies of the principal division of the medial geniculate body. The highlight of this section is the review by Suga, Kuzirai, and O'Niell of their ongoing studies of the representation of biosonar information in the auditory cortex of the mustached bat.

Under "Auditory Localization," a new view of the role of various neural structures in sound localization is outlined by Masterton, Glendenning, and Nudo. Some of their findings are replicated in a paper by Casseday and Smoak.

Several authors discussed the topic "Neural Coding of Speech and Complex Stimuli." One interesting finding from this section is that of Müller-Preuss, that some neurons in the auditory cortex of the squirrel monkey will respond differentially to the animal's own vocalization and to a recording of the same sound.

The final sections discuss "Deprivation and Developmental Studies" and "Auditory Prostheses, Physiological Background." In the first section, the 2-deoxyglucose method, auditory evoked potentials, and simple behavioral responses were used to study the onset of auditory function. For the latter topic, Keidel provides an introductory review. Two papers, presented by Tong and Clark, and by Hochmair-Desoyer et al, describe different strategies for cochlear implants and present data from patients.

The overall impression is that this volume is not as strong as previous symposium volumes have been. However, many of the contributors have addressed important but very difficult questions, and it may be unfair to expect clearcut answers in every case. On the positive side, this book does include much information about the central auditory system, while previous symposia have tended to emphasize the periphery. Thus, the reader may find it convenient to consult a single volume that provides a more comprehensive summary of the present state of auditory neurophysiology.

Donald G. Sinex, PhD
St. Louis, Missouri

Sensorineural Hearing Loss, Vertigo and Tinnitus, Vol. 1, Ear Clinics International

Edited by *Michael M. Paparella* and *William L. Meyerhoff*. Hard cover, black and white illustrations, indexed, 181 pages, 1981. Williams & Wilkins Co., Baltimore. Price $26.00.

This volume is conceived in the context of symposia for the purposes of continuing education. The first symposium celebrated the dedication of the first stage of the Lions International Hearing Center as part of the Department of Otolaryngology at the University of Minnesota. The contributions are oriented toward relatively specific problems of diagnosis, treatment and/or rehabilitation. Most of them are brief, assume the reader is only too familiar with the questions, and proceed rather directly to the appropriate answers. The contributors to this volume are all well known, and it is good fun to learn their current views. The five sections of the book are Audiological Trends, Sensorineural Hearing Loss: Medical Considerations, Hearing Aids, Tinnitus, and Vestibular Problems. Some chapters review in an up-to-date context the perspectives of thorough differential diagnoses for sensorineural and vestibular disorders to provide guides to better management of these disorders. Other chapters give status reports on old problems or on new methods of diagnosis or treatment. As might be expected, opinions differ in a number of problem areas. Nevertheless this small volume does include much good advice.

It is not possible to summarize the details of most of the contributions to this volume in a short review. However, here are examples of some of the briefer messages that do emerge. Correct medical diagnosis for every patient with sensorineural hearing loss should be based on an appreciation of temporal bone pathology and will lead to improved methods of medical or surgical therapy, habilitation and rehabilitation. Some disorders are being attributed to pathologies for which there is little or no evidence. Treatments directed against these presumed diseases are probably useless and may be harmful. The combined results of speech audiometry, acoustic reflex measurements and the auditory brainstem response can identify the location of a retrocochlear disorder even when the results of any one measure are ambiguous. Electric response audiology is here to stay.

Donald H. Eldredge, MD
St. Louis, Missouri

LETTER TO THE EDITOR

Dear Editor,

We recently published a paper in the *Annals* (Sutton D, Miller M; Cochlear implant effects on the spiral ganglion, *Ann Otol Rhinol Laryngol* 1983; 92:53-8). In that paper, I misrepresented the condition of the cochleas in a case report to which we refer. The final sentence of the initial paragraph in the paper incorrectly reads: *Both cochleas were filled with bone, and there was extensive destruction of cells in the spiral ganglion and eighth nerve axons.* The correct statement should read as follows: *Both posterior canals were undergoing ossification. The right cochlea was free of new bone but the basal turn of the left cochlea was filled with bone. Both sides exhibited extensive destruction of cells in the spiral ganglion and eighth nerve axons.*

This corrected statement exerts no influence on the conclusions of our paper, but it redresses a distortion of fact.

Dwight Sutton, PhD
Virginia Mason Research Center
Seattle

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*Ann Intern Med 1982; 96 (Part 1): 766-71.

In your rhinitis patients this season

Will antihistamine/decongestant therapy merely replace one set of symptoms with another?

The symptoms of rhinitis may be replaced by **drowsiness**

The symptoms of rhinitis may be replaced by **CNS excitation**

The symptoms of rhinitis may be replaced by **rebound congestion**

"...When effectiveness of or tolerance to conventional treatment is unsatisfactory."[1]

I. Nasalide brief summary of full prescribing information

Nasalide®
(flunisolide)

Compare Nasalide to antihistamines/decongestants

	NASALIDE (flunisolide)	ANTIHISTAMINES	ORAL DECONGESTANTS	NASAL DECONGESTANTS
Drowsiness		✗		
CNS excitation			✗	
Rebound congestion				✗

"Nuisance effects" of antihistamines/decongestants can result in noncompliance.

Drowsiness, CNS excitation and rebound congestion may interfere with your patients' jobs or daily activities. Patients who are reluctant to take a chance with these medications may not comply with therapy.

Compare Nasalide to other intranasal steroids

	NASALIDE (flunisolide)	BECONASE® (beclomethasone diproprionate)	VANCENASE® (beclomethasone diproprionate)
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Propylene glycol vehicle	✓		
Usual dosage*	**B.I.D.**	T.I.D.†	T.I.D.†

Nasalide offers effective therapy that's well tolerated by most patients.

Most frequent side effect is mild, transient nasal irritation or stinging (usually lasting only a few seconds).

See Adverse Reactions section of brief summary of full prescribing information.

*Dosage may be increased or decreased depending on severity of symptoms.

†Usual dosage range for beclomethasone is b.i.d. to q.i.d.

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Rx In seasonal and perennial rhinitis

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nasal solution 0.025%
b.i.d.

Please turn page for brief summary of full prescribing information.

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nasal solution 0.025%

Brief Summary

Description: Each bottle contains flunisolide in a solution of propylene glycol, polyethylene glycol 3350 and purified water buffered with citric acid/sodium citrate, with benzalkonium chloride added as a preservative, and NaOH and/or HCl added to adjust the pH. It contains no fluorocarbons.

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Improvement is usually apparent within a few days after starting Nasalide but may take as long as 2 weeks in some patients. Although systemic effects are minimal at recommended doses, Nasalide should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. Nasalide should not be used in the presence of untreated localized infection involving nasal mucosa.

Contraindications: Hypersensitivity to any ingredients.

Warnings: Patients transferred from systemic steroid therapy to Nasalide should be monitored to avoid acute adrenal insufficiency in response to stress. Since some patients may experience symptoms of withdrawal, attention must be given to patients previously treated for prolonged periods with systemic corticosteroids, particularly those with associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of symptoms. Nasalide should be used with caution in patients on alternate-day prednisone for any disease.

Precautions: General: Localized *Candida albicans* infections of the nose and pharynx occurred only rarely in clinical studies, but if such an infection presents, treatment with appropriate local therapy or discontinuation of Nasalide treatment may be required.

Flunisolide is absorbed into the circulation. Systemic effects have been minimal with recommended doses but larger doses should be avoided since excessive doses may suppress hypothalamic-pituitary-adrenal function.

Nasalide should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

In patients who have experienced recent nasal septal ulcers, recurrent epistaxis, nasal surgery, or trauma, a nasal corticosteroid should be used with caution until healing has occurred.

Information for Patients: Nasalide should be used as directed at the prescribed dosage. Nasal vasoconstrictors or oral antihistamines may be needed until the effects of Nasalide are fully manifested. The patient should follow the Patient Instructions carefully and should contact a physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs.

Carcinogenesis: While no evidence of carcinogenicity was found in a 22-month study in Swiss-derived mice, there was a slight increase in the incidence of pulmonary adenomas which was well within the range of spontaneous adenomas previously reported for untreated Swiss-derived mice.

Impairment of Fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in low and mid dose groups was comparable to controls.

Pregnancy: Pregnancy Category C. The drug has been shown to be teratogenic and fetotoxic in rabbits and rats. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because other corticosteroids are excreted in human milk, caution should be exercised when the drug is administered to nursing women.

Adverse Reactions: The most frequent complaints were mild transient nasal burning and stinging (reported in approximately 45% of patients). These complaints do not usually interfere with treatment; in only 3% of patients was it necessary to decrease dosage or stop treatment because of those symptoms.

Incidence of 5% or less: nasal congestion, sneezing, epistaxis and/or bloody mucus, nasal irritation, watery eyes, sore throat, nausea and/or vomiting, headaches and loss of sense of smell and taste. In rare instances, nasal septal perforations were observed during the studies but a causal relationship with Nasalide was not established.

Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded, or if individuals are particularly sensitive, symptoms of hypercorticism could occur.

Dosage and Administration: Full therapeutic benefit requires regular use and is usually evident within a few days, but up to 3 weeks may be required for some patients to achieve maximum benefit. Patients should use a decongestant and clear their nasal passages of secretions prior to use.

Recommended starting dose in adults: 2 sprays in each nostril b.i.d. If needed, increase to 2 sprays t.i.d.

Recommended starting dose in children (6-14 years): 1 spray in each nostril t.i.d. or 2 sprays in each nostril b.i.d. Not recommended for use in children less than 6 years old.

Total daily doses: not to exceed 8 sprays in each nostril for adults and 4 sprays in each nostril for children.

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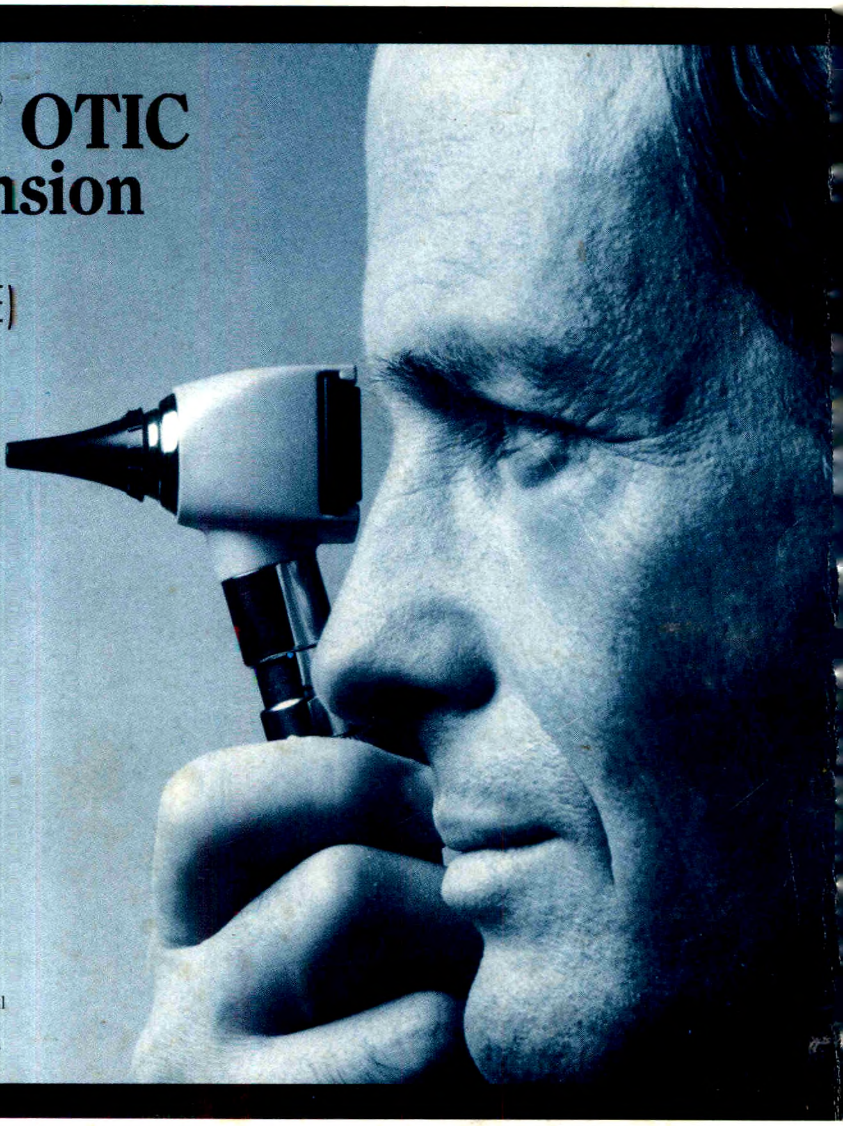

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Total ears	107
Responders	104 (97.2%)
Combined suspension and solution	
Total ears	200
Responders	195 (97.5%)

Adapted from Cassisi et al.[1]

REFERENCE:

1. Cassisi N, Cohn A, Davidson T, et al: Diffuse otitis externa: Clinical and microbiologic findings in the course of a multicenter study on a new otic solution. *Ann Otol Rhinol Laryngol* 86(suppl 39, pt 3):1-16, 1977.

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Precautions: This drug should be used with care in cases of perforated eardrum and in long-standing cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

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Description: Each cc contains:
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The vehicle contains the inactive ingredients cupric sulfate, glycerin, hydrochloric acid, propylene glycol, water for injection and potassium metabisulfite (preservative) 0.1%.

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Precautions: This drug should be used with care when the integrity of the tympanic membrane is in question because of the possibility of ototoxicity caused by neomycin.

Adverse Reactions: Stinging and burning have been reported when this drug has gained access to the middle ear.

Contraindications, Warnings, Precautions and Adverse Reactions Common to Both Products

Contraindications: These products are contraindicated in those individuals who have shown hypersensitivity to any of the components, and in herpes simplex, vaccinia and varicella.

Warnings: As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi. If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

Precautions: If sensitization or irritation occurs, medication should be discontinued promptly. Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

Treatment should not be continued for longer than ten days. Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

Adverse Reactions: Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

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